Medicaid Dossier for *Avandia*

This information is provided in response to your request for information about Avandia® (rosiglitazone maleate).

Some information contained in this response may not be included in the approved Prescribing Information. This response is not intended to offer recommendations for administering this product in a manner inconsistent with its approved labeling.

In order for GlaxoSmithKline to monitor the safety of our products, we encourage healthcare professionals to report adverse events or suspected overdoses to the company at 888-825-5249. Please consult the attached Prescribing Information.

This response was developed according to the principles of evidence-based medicine and, therefore, references may not be all-inclusive.

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The purpose of the Change Summary is to provide a description of the significant changes/revisions to the dossier from the previous version(s). The following indicates sections within the dossier that where new clinical data has been added to the dossier within the past year:

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2. PRODUCT SUMMARY

About Type 2 Diabetes

- Over 23 million people in the United States have diabetes. Type 2 diabetes accounts for 90-95% of all diagnosed cases. [1]
- Type 2 diabetes is considered one of the most costly diseases in the United States, in part due to its association with microvascular and macrovascular complications.[2]
- Approximately 90% of patients with type 2 diabetes are insulin resistant.[3,4]
- Type 2 diabetes is characterized by a progressive loss of glycemic control marked by an increase in insulin resistance and decline in beta-cell function.[5,6]

About *Avandia*

- *Avandia* is a thiazolidinedione (TZD) indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes as monotherapy or combination therapy with metformin and/or sulfonylurea (SU).[7]

Glycemic Efficacy and Safety

- ADOPT (*A D*iabetes *O*utcome *P*rogression *T*rial) evaluated the efficacy of *Avandia*, metformin, or glyburide as initial therapy in maintaining glycemic control in 4,360 recently diagnosed (<3 yrs) type 2 diabetes patients inadequately controlled with diet and exercise alone (median treatment period: 4 years).[8]
  - There was a 32% risk reduction in the primary outcome of time to monotherapy failure [fasting plasma glucose (FPG) > 180 mg/dl] with *Avandia* compared to metformin ($P < 0.001$) and a 63% risk reduction with *Avandia* compared to glyburide ($P < 0.001$).[8] The cumulative incidence of the primary efficacy outcome at 5 years was 15% with *Avandia*, 21% with metformin, and 34% with glyburide.[7]
  - Additionally, there was a 36% risk reduction in the secondary outcome of time to progression to FPG > 140mg/dl with *Avandia* compared to metformin ($P = 0.002$) and a 62% risk reduction with *Avandia* compared to glyburide ($P < 0.001$).[8] Mean A1C < 7% was sustained for 57 months with *Avandia*, 45 months with metformin, and 33 months with glyburide.
  - Cardiovascular adverse events were reported in 4.3% (n = 62) of participants receiving *Avandia*, 4.0% (n = 58) in the metformin group, and 2.8% (n = 41) in the glyburide group.[8] Investigator-reported congestive heart failure (CHF) occurred in 1.5% (n = 22), 1.3% (n = 19), and 0.6% (n = 9) of participants receiving *Avandia*, metformin, and glyburide, respectively ($P \leq 0.05$ *Avandia* vs glyburide). Edema was reported in 14.1% of participants receiving *Avandia*, 7.2% of participants receiving metformin, and 8.5% of participants receiving glyburide ($P \leq 0.01$ *Avandia* vs glyburide and vs metformin). Gastrointestinal events were less frequently reported with *Avandia* (23%) as compared to metformin (38.3%; $P \leq 0.01$). Hypoglycemia was less frequently reported with *Avandia* (9.8%) than metformin (11.6%) and glyburide (38.7%; $P \leq 0.01$).
  - A post-study ad hoc analysis was conducted to evaluate the ischemic cardiovascular safety events in ADOPT. [7,9] The analysis suggests that the risk of myocardial infarction [(MI); adjudicated fatal and nonfatal MI plus sudden death], major adverse cardiovascular events [(MACE); cardiovascular death, MI, stroke], and total mortality in patients exposed to *Avandia* were not significantly different to those exposed to either metformin or sulfonylurea.
  - Over the 4 to 6 year period, the incidence of bone fracture in females was 9.3% (60/645) for *Avandia* versus 3.5% (21/605) for glyburide and 5.1% (30/590) for metformin.[7,8] This increased incidence was noted after the first year of treatment and persisted during the course of the study. The majority of fractures in the women who received *Avandia* occurred in the upper arm, hand, and foot. These sites of fracture are different from those usually associated with postmenopausal osteoporosis (e.g., hip or spine). No increase in fracture rates was observed in men treated with *Avandia*.

- As part of its ongoing monitoring and assessment of the safety of *Avandia*, GlaxoSmithKline (GSK) proactively conducted a series of retrospective analyses to characterize the degree of association, if any, between *Avandia* and events of CHF and myocardial ischemia.[10] Forty-two controlled and blinded clinical trials that included 4 mg or 8 mg doses of *Avandia* were included in the analysis.
  - In the Integrated Clinical Trials (ICT) analysis, an increased risk of myocardial ischemia with *Avandia* versus pooled comparators was observed (1.99% *Avandia* versus 1.51% comparators, hazard ratio (HR) 1.31, 95% confidence interval [CI] 1.01, 1.70).[10,11] An increased risk of myocardial ischemic events with *Avandia* was observed in the placebo-controlled studies, but not in the active-controlled studies. The hazard ratios for myocardial ischemic events for *Avandia* compared to placebo and active controls were 1.68 [95% CI: 1.22-2.32] and 1.01 (95% CI: 0.64-1.58), respectively. An increased risk of myocardial ischemic events was observed in the subset of patients with *Avandia* added to insulin therapy and in patients receiving *Avandia* and background nitrate therapy.
  - A separate analysis by the FDA on this same set of clinical trials yielded similar results (*Avandia* versus pooled comparators, odds ratio 1.4, 95% CI 1.1, 1.8). [7]
- Analyses of the data from ADOPT, DREAM, and RECORD, involving 14,067 subjects with 21,803 patient-years exposure to *Avandia* and 25,998 patient-years exposure to comparators, showed no statistical difference between *Avandia* and comparators for myocardial infarction, MACE, and total mortality.[7]

ADDITIONAL CLINICAL INFORMATION

- In a retrospective data analysis, *Avandia* (n = 99), pioglitazone (n = 98), and troglitazone (no longer marketed; n = 90), were evaluated in 287 patients with type 2 diabetes previously treated with a TZD for ≥ 300 and ≤ 900 days.[12] The analysis was conducted to determine the long-term effects on glycemic control, lipid parameters, blood pressure, weight, edema, and liver function.
  - There was no significant differences among treatment groups at baseline with a mean age of ~ 58.6 yrs and duration of diabetes ~ 10.8 years. [12] Additionally, there were no significant differences with regard to lipid parameters at baseline (mean total cholesterol (TC) = 195.5 mg/dl; mean low-density lipoprotein (LDL) = 112.3 mg/dl; mean high-density lipoprotein (HDL) = 45.6 mg/dl; mean triglycerides (TG) = 262.5 mg/dl). Significant decreases were observed for TC, LDL, and TG upon initiation of a TZD in each treatment group. A statistically significant increase in HDL was reported in patients receiving *Avandia* or pioglitazone as compared to troglitazone. There were no statistically significant differences among the treatment groups with regard to TC, LDL, or TG.
  - The most common subjectively reported adverse events included weight gain, edema, hypoglycemia, and dyspnea. There were no significant differences among adverse events between *Avandia*, pioglitazone, and troglitazone treatment groups.[12]
  - TZDs are not FDA-approved for the management of dyslipidemia. As such, GlaxoSmithKline supports the American Diabetes Association (ADA) recommendations stating that patients with diabetes and dyslipidemia initiate lifestyle interventions and take lipid-lowering therapy as appropriate.[13]

Ongoing Trials

- RECORD (*R*osiglitazone *E*valuated for *C*ardiac *O*utcomes and *R*egulation of Glycemia in *D*iabetes) is a long-term, randomized, multicenter, open-label, noninferiority study involving 4447 patients with type 2 diabetes.[14]The study was designed to prospectively compare CV outcomes in patients with type 2 diabetes treated with *Avandia* plus metformin or sulfonylurea (*Avandia* group) with outcomes in patients treated with metformin plus sulfonylurea (control group). An unplanned interim analysis was conducted to evaluate cardiovascular (CV) outcomes.
  - There was no significant difference between the *Avandia* group and the control group in the adjudicated primary endpoint of CV hospitalization and death.[14] A total of 217 patients in the *Avandia* group and 202 patients in the control group experienced the adjudicated primary endpoint (HR, 1.08; 95% CI, 0.89 to 1.31). After the inclusion of endpoints for an additional 91 patients (50 in the *Avandia* group and 41 in the control group) pending adjudication, the

hazard ratio was 1.11 (95% CI, 0.93 to 1.32). Overall, the rate of the primary endpoint (CV hospitalization or death) was low: 3.1% per year for adjudicated plus pending events.

- For the secondary endpoints of myocardial infarction, death from CV or any cause (total mortality), or the composite of CV death, myocardial infarction, and stroke, referred to as major adverse cardiovascular events (MACE), there was no statistically significant differences between the *Avandia* group and the control group. (7,14) Patients in the *Avandia* group had a significantly higher risk of CHF than did patients in the control group, with 38 versus 17 adjudicated events (HR, 2.24; 95% CI, 1.27 to 3.97).
- The interim analysis of RECORD showed that the *Avandia* group was not significantly different from the control group in the primary endpoint of CV hospitalization or death.(14) Due to the limited power of the interim analysis, which was based on data for 4447 patients with a mean follow-up of 3.75 years, a conclusion on the primary endpoint must await study completion which is anticipated in late 2008. Additionally, the data do not allow a conclusion on the relative risks of myocardial infarction among the medications studied.

- In the latter half of 2007, Independent Drug Safety Monitoring Boards determined that the following ongoing, long-term, prospective clinical trials involving over 17,000 patients should continue:(14,15,16)
  - APPROACH (*A*sessment on the *P*revention of *P*rogression by *R*osiglitazone *O*n *A*therosclerosis in Diabetes Patients with *C*ardiovascular *H*istory)
  - RECORD (*R*osiglitazone *E*valuated for *C*ardiac *O*utcomes and *R*egulation of Glycemia in *D*iabetes)
  - BARI-2D (*B*ypass *A*ngioplasty *R*evascularization *I*nvestigation *2 D*iabetes)
  - ACCORD (*A*ction to *C*ontrol *C*ardi*O*vascular *R*isk in *D*iabetes)

OUTCOMES TRIALS

- Data from two major diabetes outcomes trials examining cardiovascular effects of intensive glucose lowering in type 2 diabetes were presented at the 68th Annual Scientific Sessions of the American Diabetes Association (ADA) . These included:
  - VADT (*V*eterans *A*ffairs *D*iabetes *T*rial: glycemic control and complications in diabetes mellitus type 2)
  - ACCORD Interim Analysis
- While the studies were not prospectively designed to assess the safety of *Avandia*, the investigators of VADT and ACCORD, two independent, long-term CV outcomes studies involving over 20,000 years of patient experience with rosiglitazone in a high risk population, found that *Avandia* was not related to any increased risk of mortality.(17,18)

Pharmacoeconomic Data

- A retrospective cohort study was conducted using patient data from the North Carolina Medicaid program database queried from July 1, 2001 to June 30, 2002. (19) Patients were followed up for complete healthcare service utilization (hospitalizations, emergency department visits, outpatient physician visits, utilization of antidiabetic medication) and costs.
  - Measures of adherence (medication possession ratio) and persistence (index of treatment persistence) were used to assess utilization of antidiabetic medication. (19) Total annual healthcare costs were compared for Medicaid recipients newly started on TZDs vs. other oral antidiabetic agents. Patients starting TZDs had 16% lower total annual healthcare costs compared to patients starting other oral antidiabetics ($P < 0.05$). The persistence and adherence rates for the TZD group were statistically significantly higher than the oral antidiabetics group at nearly 9% and 13%, respectively ($P < 0.01$). The subanalysis comparing the two TZDs, *Avandia* and pioglitazone, showed no significant differences between the two TZD groups in total annual healthcare costs, treatment adherence, or persistence rates.

Important Clinical Considerations for *Avandia*

Avandia is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes.

Important Limitations of Use:

- Coadministration of *Avandia* and insulin is not recommended
- Use of *Avandia* with nitrates is not recommended

CONTRAINDICATION:

- Initiation of *Avandia* in patients with established New York Heart Association (NYHA) Class III or IV heart failure

Boxed WARNING: CONGESTIVE HEART FAILURE AND MYOCARDIAL ISCHEMIA

- Thiazolidinediones, including rosiglitazone, cause or exacerbate congestive heart failure in some patients. Observe patients carefully for signs and symptoms of heart failure (including excessive, rapid weight gain, dyspnea, and/or edema). If these develop, the heart failure should be managed according to current standards of care. Discontinuation or dose reduction of *Avandia* must be considered
- *Avandia* is not recommended in patients with symptomatic heart failure
- A meta-analysis of 42 clinical studies (mean duration 6 months; 14,237 total patients), most of which compared *Avandia* to placebo, showed *Avandia* to be associated with an increased risk of myocardial ischemic events such as angina or myocardial infarction. Three other studies (mean duration 41 months; 14,067 total patients), comparing *Avandia* to some other approved oral antidiabetic agents or placebo, have not confirmed or excluded this risk. In their entirety, the available data on the risk of myocardial ischemia are inconclusive

OTHER WARNINGS AND PRECAUTIONS

- Initiation of *Avandia* is not recommended for patients experiencing an acute coronary event and discontinuation of *Avandia* during this event should be considered
- Dose-related edema, weight gain, and anemia may occur
- *Avandia* should not be started in patients with active liver disease or with ALT levels >2.5X the upper limit of normal. Check liver enzymes prior to initiation of *Avandia* and periodically per clinical judgment
- *Avandia*, in combination with other hypoglycemic agents, may increase the risk of hypoglycemia
- Macular edema has been reported
- Increased incidence of bone fracture in female patients
- Resumption of ovulation can occur

3. DISEASE DESCRIPTION

Epidemiology and Risk Factors

Over 23 million people (7.8% of the population) in the United States have diabetes.[1] Of these, 5.7 million people are not aware that they have the disease. Diabetes was the seventh deadliest disease in the United States in 2006 and is associated with a number of serious microvascular and macrovascular complications.

Type 2 diabetes accounts for 90-95 % of all diagnosed cases of diabetes.[1] The major risk factors for developing type 2 diabetes include a family history of diabetes, overweight or obesity, physical inactivity, race/ethnicity, previously identified impaired glucose tolerance or impaired fasting glucose, hypertension, low high-density lipoprotein (HDL) cholesterol or high triglycerides, a history of gestational diabetes mellitus or delivering a baby weighing > 9 pounds, polycystic ovary syndrome, and a history of cardiovascular disease.[20]

Pathophysiology

Diabetes mellitus is a group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both. [21] Type 2 diabetes results from insulin resistance (primarily at the liver, skeletal muscle, and adipose tissue), combined with impaired insulin secretion.[22] Over 90% of patients with type 2 diabetes are insulin resistant. [23] Insulin resistance is often detectable 15 to 20 years before the onset of type 2 diabetes.[24] In addition to being associated with type 2 diabetes, insulin resistance is also believed to be associated with a cluster of metabolic abnormalities that include impaired glucose tolerance, hypertension, abdominal obesity, dyslipidemia, and prothrombotic and proinflammatory states.[25] Collectively, these components are known as the metabolic syndrome.

When the peripheral tissues do not adequately respond to insulin, there is decreased peripheral glucose uptake.[26] This causes circulating blood glucose concentrations to rise. The resulting hyperglycemia then stimulates the pancreas to augment insulin secretion, leading to hyperinsulinemia. Early in the disease course but before the development of type 2 diabetes, the pancreas is able to overcome insulin resistance and maintain euglycemia. However, as the disease progresses to impaired glucose tolerance and type 2 diabetes, the pancreas is no longer able to provide enough insulin to overcome the body's resistance and hyperglycemia develops.

Clinical Presentation

Type 2 diabetes is often asymptomatic in its early stages and therefore can remain undiagnosed for many years.[20] However, patients experiencing symptoms can present with complaints of frequent urination, unusual thirst, extreme hunger, unusual weight loss, extreme fatigue, irritability, frequent infections, blurred vision, cuts/bruises that are slow to heal, tingling/numbness in the hands or feet, and recurring skin, gum, or bladder infections.[2] [21]Many patients remain undiagnosed until they present with one of the complications of diabetes. Long-standing hyperglycemia may result in microvascular complications including retinopathy, nephropathy, and neuropathy or macrovascular complications including cardiovascular disease, cerebrovascular disease, and peripheral vascular disease.

Current American Diabetes Association (ADA) recommendations for the diagnosis of type 2 diabetes are available at www.diabetes.org.

Approaches to Treatment-Principle Options/Practice Patterns/Place in Therapy

The management plan for a patient with diabetes should be individualized based on several patient characteristics including age, eating patterns, physical activity, presence of complications, etc. [20] Lifestyle modifications (i.e., diet, exercise, and weight loss) should be the center of any therapeutic program since they have been shown to lower glucose concentrations and may help improve risk factors for microvascular complications and possibly cardiovascular disease. [27]

Pharmacologic treatment of type 2 diabetes includes oral antidiabetic medications that focus mainly on increasing insulin secretion, decreasing hepatic glucose production, or reducing insulin resistance. [27] A summary of the different classes of oral antidiabetic agents is included in Table 1.

Maintaining glycemic control is a key goal in helping to minimize the complications associated with type 2 diabetes. Currently, glycemic treatment goals recommended by the ADA include an A1c of <7%, preprandial plasma glucose of 70-130 mg/dL, and peak postprandial plasma glucose <180 mg/dL.[20] The American Association of Clinical Endocrinologists (AACE) recommends an A1c of ≤ 6.5%, preprandial glucose of ≤ 110 mg/dL, and postprandial glucose ≤ 140 mg/dL.[28] Since diabetes is a progressive disease, the majority of patients will often require more than one medication to treat their diabetes. [29] [30] Data from the United Kingdom Prospective Diabetes Study (UKPDS) found that the proportion of patients able to maintain target glycemic levels with diet, insulin, sulfonylurea, or metformin declined markedly over 9 years of follow-up (~50% of patients achieved target after 3 years of monotherapy; ~25% of patients achieved target after 9 years of monotherapy).[29] Thus, the ability of an agent to maintain glycemic control over the long-term is an important consideration when choosing therapy. If glycemic control cannot be maintained with oral agents alone, insulin may be added as well. [31] There are many obstacles to maintaining glycemic control in type 2 diabetes. Therefore, combination therapy should be promptly initiated.[32]

Table 1. Therapeutic Options for the Treatment of Type 2 Diabetes(27,32,33,34,35,36,37,38,7,39,40,41,42,43,44)

Class	**Mechanism of Action**	**Advantages**	**Limitations**	**FDA Indications**
Sulfonylureas • glyburide, glipizide, glimepiride	↑ insulin secretion from the pancreas	-Decreases microvascular risk -Convenient daily dosing -Immediate onset of action	-Hypoglycemia -Weight gain -Hyperinsulinemia - Potential increased CV mortality risk	Monotherapy, Combo with insulin, metformin. TZDs, or α-glucosidase inhibitors
Biguanides • metformin	Primary ↓ hepatic glucose production	-Weight loss -No hypoglycemia as monotherapy -Decreases macrovascular risk -Potential nonglycemic benefits -Convenient daily dosing	-Adverse GI effects -Contraindicated in patients with renal disease -Contraindicated in patients with CHF requiring pharmacologic treatment -Contraindicated in patients with acute or chronic metabolic acidosis, including diabetic ketoacidosis, with or without coma -Lactic acidosis risk (rare) -Should be temporarily discontinued in patients undergoing radiologic studies involving intravascular administration of iodinated contrast materials	Monotherapy, Combo with insulin, SU, meglitinides, or TZDs

*This table is not meant to represent a comprehensive review of these agents. Please refer to the respective Prescribing Information for full details regarding these products; †As measured by homeostasis model assessment (HOMA). Combo = combination therapy; CV = cardiovascular; CHF = congestive heart failure; DPP-4 = dipeptidyl peptidase-4; GI = gastrointestinal; GLP-1 = glucagon-like peptide-1; LFT = liver function test; PPG = post-prandial glucose; T2DM = type 2 diabetes mellitus; TZD = thiazolidinedione; SU = sulfonylurea; SCr = serum creatinine; ESRD = end stage renal disease.

Class	**Mechanism of Action**	**Advantages**	**Limitations**	**FDA Indications**
α-glucosidase inhibitors • acarbose, miglitol	↓ absorption of carbohydrates in the gut	-Targets PPG -No hypoglycemia as monotherapy -Nonsystemic	-Dosed 3X/day -Adverse GI effects -No long term data -LFT monitoring (acarbose) -Limited information on severely renal impaired patients, SCr > 2.0 mg/dL, therefore, treatment not recommended -Contraindicated in patients with inflammatory bowel disease, colonic ulceration or partial intestinal obstruction and in patients predisposed to intestinal obstruction -Contraindicated in patients with chronic intestinal diseases associated with disorders of digestion or absorption, or conditions that may deteriorate as a result of increased gas formation in the intestine	Monotherapy, Combo with SU

*This table is not meant to represent a comprehensive review of these agents. Please refer to the respective Prescribing Information for full details regarding these products; †As measured by homeostasis model assessment (HOMA). Combo = combination therapy; CV = cardiovascular; CHF = congestive heart failure; DPP-4 = dipeptidyl peptidase-4; GI = gastrointestinal; GLP-1 = glucagon-like peptide-1; LFT = liver function test; PPG = post-prandial glucose; T2DM = type 2 diabetes mellitus; TZD = thiazolidinedione; SU = sulfonylurea; SCr = serum creatinine; ESRD = end stage renal disease.

Class	**Mechanism of Action**	**Advantages**	**Limitations**	**FDA Indications**
Thiazolidinediones (TZDs) • rosiglitazone, pioglitazone	Insulin sensitizer, ↑ peripheral glucose disposal	-Minimal risk of hypoglycemia as monotherapy -Targets insulin resistance, a core defect of T2DM - Improves estimates of β-cell function	-Boxed Warning for Congestive Heart Failure -Boxed Warning for Myocardial Ischemia with rosiglitazone -Coadministration of rosiglitazone with insulin is not recommended -Use of rosiglitazone with nitrates is not recommended -Initiation of rosiglitazone is not recommended for patients experiencing an acute coronary event, discontinuation during this acute phase should be considered -Macular edema -Bone fracture -LFT monitoring -Weight gain, edema -Decrease in hemoglobin and hematocrit Rosiglitazone, in combination with other hypoglycemic agents, may increase the risk of hypoglycemia -Increased risk of pregnancy in premenopausal anovulatory women	Monotherapy, Combo therapy with metformin and/or SU
Meglitinides/D-phenylalanine derivatives • nateglinide, repaglinide	↑ insulin secretion from the pancreas	-Targets PPG - Possible less hypoglycemia and weight gain than with SUs	-Dosed 3X/day -Hypoglycemia -Weight gain - Hyperinsulinemia -No long term data - Upper respiratory tract infection	Monotherapy, Combo with metformin or TZDs

*This table is not meant to represent a comprehensive review of these agents. Please refer to the respective Prescribing Information for full details regarding these products; †As measured by homeostasis model assessment (HOMA). Combo = combination therapy; CV = cardiovascular; CHF = congestive heart failure; DPP-4 = dipeptidyl peptidase-4; GI = gastrointestinal; GLP-1 = glucagon-like peptide-1; LFT = liver function test; PPG = post-prandial glucose; T2DM = type 2 diabetes mellitus; TZD = thiazolidinedione; SU = sulfonylurea; SCr = serum creatinine; ESRD = end stage renal disease.

Class	Mechanism of Action	Advantages	Limitations	FDA Indications
Incretin mimetics/ GLP-1 analogues • exenatide	↑ insulin secretion from the pancreas, ↓ glucagon secretion from the pancreas	-Sustained glycemic control -Weight loss -Improves estimates of β-cell function	-Subcutaneous injection -Dosed twice daily -Adverse GI side effects - Post-marketing reports of acute pancreatitis Not recommended in patients with ESRD	Combo with metformin, SU, or TZD Combo with metformin and SU, or metformin and TZD
Dipeptidyl peptidase-4 (DPP-4) inhibitors • sitagliptin	Slow inactivation of GLP-1 ↑ insulin secretion from the pancreas, ↓ glucagon secretion from the pancreas	-No weight gain -Less hypoglycemia than SU's Good tolerability profile Improves estimates of β-cell function	-Possibility for neurogenic and allergic reactions (theoretical) -Tolerability decreased with decreased DPP-4 specificity - Upper respiratory tract infections, nasopharyngitis, headache - Dosage adjustment with moderate or severe renal insufficiency	Monotherapy, Combo with metformin or TZD
*This table is not meant to represent a comprehensive review of these agents. Please refer to the respective Prescribing Information for full details regarding these products; †As measured by homeostasis model assessment (HOMA). Combo = combination therapy; CV = cardiovascular; CHF = congestive heart failure; DPP-4 = dipeptidyl peptidase-4; GI = gastrointestinal; GLP-1 = glucagon-like peptide-1; LFT = liver function test; PPG = post-prandial glucose; T2DM = type 2 diabetes mellitus; TZD = thiazolidinedione; SU = sulfonylurea; SCr = serum creatinine; ESRD = end stage renal disease.				

Description of Alternate Treatment Options

The available literature demonstrates that several commonly used natural products can lower blood glucose in patients with diabetes. These products include N-acetylcysteine (NAC), pomegranate, coenzyme Q10, vitamin C, vitamin D, vitamin E, green tea, lutein, zeaxanthin, L-carnitine, cinnamon, magnesium, vanadium sulfate, nopal (prickly pear cactus), fenu-greek, karela (bitter melon), gymnema, ginseng, tronadora, chromium, and alpha-lipoic acid.[45,46]

Gene therapy/transplant (pancreas, islet cell) have more commonly been utilized in type 1 diabetes, but preliminary studies have evaluated its use in type 2 diabetes.[47]

4. PRODUCT DESCRIPTION

4.1 Generic Name, Brand Name and Therapeutic Class

Generic Name: Rosiglitazone maleate

Brand Name: Avandia®

Therapeutic Class: Thiazolidinedione class of antidiabetic agents

4.2 Dosage Forms, Package Sizes, NDC

Dosage Forms/National Drug Code:

- 2 mg strength:
  - bottles of 60: 0029-3158-18
- 4 mg strength:

  - bottles of 30: 0029-3159-13
  - bottles of 90: 0029-3159-00
- 8 mg strength:
  - bottles of 30: 0029-3160-13
  - bottles of 90: 0029-3160-59

4.3 AWP and WAC Cost per Unit

Wholesaler Acquisition Cost (WAC) per tablet:

- 2 mg: $2.11
- 4 mg: $3.14
- 8 mg: $5.70

4.4 AHFS or Other Drug Classification

AHFS Drug Classification:

- 68:20.92 Miscellaneous Antidiabetic Agents

4.5 FDA Approved Indications

General

Refer to Enclosed Prescribing Information.

Date of FDA Approval

Date of FDA Approval:

- *Avandia* as monotherapy: May 25, 1999
- *Avandia* 4 or 8 mg/day in combination with metformin: May 25, 1999
- *Avandia* 4 mg/day in combination with a sulfonylurea: April 3, 2000
- *Avandia* 8 mg/day in combination with a sulfonylurea: February 28, 2005
- *Avandia* in combination with a sulfonylurea plus metformin: February 28, 2005

4.6 Use in Special Populations

Use of Avandia in Elderly Patients with Type 2 Diabetes

Efficacy and Safety of *Avandia* in Elderly Patients

Monotherapy

Data was pooled from three double-blind, monotherapy studies with *Avandia* to evaluate the effects of age on treatment response.[48,49,50] The pooled data included two 26-week, placebo-controlled trials (Studies 011 and 024) and a 52-week, active-controlled trial (Study 020). During the monotherapy trials, *Avandia* produced similar effects on fasting plasma glucose (FPG) and HbA1c in patients $\geq$ 65 years (n = 545) to those observed in younger patients (< 65 years; n = 1239). Please refer to Table 2.

Table 2. Change (Mean ± SD) in FPG (mg/dL) and HbA1c (%) from Baseline to Week 26 by age with Monotherapy(48,49,50)*

Age	Placebo	*Avandia* 2 mg BID	*Avandia* 4 mg QD	*Avandia* 4 mg BID	*Avandia* 8 mg QD
< 65 years	**n = 234**	**n = 383**	**n = 133**	**n = 365**	**n = 124**
FPG	14 ± 57.6	-34 ± 47.3	-21 ± 59.1	-50 ± 48.0	-42 ± 62.4
HbA1c	0.8 ± 1.2	-0.3 ± 1.3	0 ± 1.5	-0.6 ± 1.3	-0.3 ± 1.3
≥ 65 years	**n = 97**	**n = 164**	**n = 47**	**n = 180**	**n = 57**
FPG	12 ± 54.9	-43 ± 45.1	-34 ± 48.6	-56 ± 49.5	-43 ± 45.0
HbA1c	0.9 ± 1.1	-0.3 ± 1.1	0.1 ± 1.1	-0.53 ± 1.3	-0.27 ± 1.2

*Pooled data from two 26-week, placebo controlled trials and a 52-week, active controlled trial.

BID = twice daily; FPG = fasting plasma glucose; QD = once daily; SD = standard deviation

In terms of treatment effect, data from the two 26-week, monotherapy trials (Studies 011 and 024) indicate that *Avandia* 4 and 8 mg/day produced similar effects on FPG and HbA1c in patients ≥ 65 years and patients < 65 years.(48,49)

During the pre-approval, double-blind trials evaluating *Avandia* as monotherapy, 33% of the 2526 patients evaluated were ≥ 65 years of age.(51,52,48,49,50,53,54,55) In monotherapy trials, the proportion of patients ≥ 65 years of age experiencing at least one adverse event was similar to the proportion of patients < 65 years of age. (56) The most common adverse events occurring in patients ≥ 65 years of age treated with *Avandia* monotherapy are listed in Table 3.

Table 3. Adverse Events Reported by Age During the Monotherapy Studies for *Avandia*(51,52,48,49,50,53,54,55,56)

	Avandia Monotherapy		Placebo	
	< 65 years (n = 1694)	**≥ 65 years (n = 832)**	**< 65 years (n = 404)**	**≥ 65 years (n = 197)**
URTI	11.1%	7.6%	9.4%	7.1%
Injury*	7.7%	7.5%	4.7%	3.6%
UTI	3.2%	4.9%	2.7%	3.6%
Back pain	3.7%	4.7%	3.2%	5.1%
Hyperglycemia	3.7%	4.4%	5.4%	6.1%
Headache	6.7%	4.2%	5.0%	5.1%

* Includes items such as cuts, burns, sprains, fractures, accidents and surgical procedures.

URTI = Upper respiratory tract infection; UTI = Urinary tract infection.

In addition to the adverse events listed above, edema occurred in 3.5% and 7.5% of patients < 65 years and ≥ 65 years old treated with *Avandia* alone, respectively, and in up to 1.7% of patients on placebo. (56) Monotherapy with *Avandia* was also associated with anemia, which occurred in 1.7% and 2.5% of patients < 65 and ≥ 65 years old, respectively, and in up to 1% of patients receiving placebo. Less than 1% of patients receiving *Avandia* as monotherapy reported hypoglycemia, regardless of age.

Observational Cardiovascular Safety Data in Elderly Patients

A population-based, retrospective nested case-control cohort study was conducted using health care databases from Ontario, Canada to evaluate the risks of congestive heart failure (CHF), acute myocardial infarction (MI), and all-cause mortality associated with the use of thiazolidinediones (TZDs) compared to other oral hypoglycemic drug combination therapies.(57) Of note, reimbursement for TZDs during the time of the study was restricted to patients experiencing uncontrolled hyperglycemia or to those who had a contraindication or intolerance to metformin and/or sulfonylureas. The study population included diabetic patients from Ontario who were 66 years of age or older treated with at least 1 oral hypoglycemic drug between April 1, 2002 and March 31, 2005. Patients who were treated with insulin in the year prior to cohort entry were excluded, while patients who began treatment with insulin during follow-up were retained in the study.

The study population consisted of 159,026 diabetic patients who were treated with oral hypoglycemic agents.(57) The mean age of the individuals included in the study was 74.7 years, and the median follow-up for the study was 3.8 years. A greater proportion of patients taking TZD monotherapy had a history of renal and cardiovascular disease compared with those receiving TZD combination therapy and other oral antidiabetic agent combination therapy. Patients receiving *Avandia* monotherapy had greater comorbidity compared with those prescribed pioglitazone monotherapy, although the proportion with a history of cardiovascular disease was similar. All other baseline characteristics were similar between the groups. Overall, 7.9% of patients (n = 12,491) had a hospital visit for CHF, 7.9% for acute MI (n = 12,578), and 19% died (n = 30,265). Compared with patients receiving other oral hypoglycemic agent combination therapy, current users of TZD monotherapy [adjusted rate ratio (RR), 1.60; 95% confidence interval (CI) 1.21-2.10; P<0.001] and combination therapy (adjusted RR, 1.31; 95% CI, 1.17-1.47; P<0.001) were at an increased risk of CHF. An increased risk of acute MI was seen with current use of TZD monotherapy (adjusted RR, 1.40; 95% CI, 1.05-1.86; P=0.02), but not TZD combination therapy (adjusted RR, 0.96; 95% CI, 0.85-1.08; P=0.49) compared to use of other oral hypoglycemic agent combinations. Both TZD monotherapy (adjusted RR, 1.29; 95% CI, 1.02-1.62; P=0.03) and combination therapy (adjusted RR, 1.24; 95% CI, 1.11-1.39; P<0.001) were associated with an increased risk of death compared to other oral hypoglycemic agent combination therapies. The association between CHF, acute MI, and mortality and TZD therapy appeared to be limited to treatment with *Avandia*; however, there was limited power to explore the association between outcomes and the use of pioglitazone due to the smaller number of patients taking pioglitazone.

Pharmacokinetic Data in Elderly Patients

The pharmacokinetic profile of *Avandia* in elderly subjects was evaluated in an open-label, single-dose trial which included 10 healthy, elderly (≥ 65 years) males and 10 healthy, young (18 - 45 years) males.(58) Following a single dose of *Avandia* 4 mg under fasted conditions, mean Tmax (~1 hour in both groups) and mean $T_{1/2}$ (3.9 hours vs. 4.2 hours, respectively) were similar among the elderly and young subjects.(59) The maximum plasma concentration was 38% lower in patients ≥ 65 years of age (170 ng/mL) than patients < 65 years of age ((273 ng/mL) [95% CI (0.48, 0.81)]).(58) Additionally, $AUC_{(0\text{-inf})}$ was 36% lower in the elderly (998 ng • h/mL) compared to younger subjects (1563 ng ≥ h/mL) [95% CI (0.46, 0.88)].

In an analysis of population pharmacokinetics (n = 716 < 65 years; n = 331 ≥ 65 years), age did not significantly affect the pharmacokinetics of *Avandia* in diabetic patients; therefore, no dosage adjustments are necessary in the elderly.(7)

Use of Avandia in Pediatric Patients

Avandia is not indicated for use in pediatric patients with type 2 diabetes; data are insufficient to recommend pediatric use of *Avandia*.(7) GlaxoSmithKline cannot make any specific recommendations regarding the use of *Avandia* in patients under 18 years of age.

In a double-blind, controlled study, children with type 2 diabetes mellitus, aged 10 to 17 years and with a baseline mean body mass index (BMI) of 33 kg/m^2, were randomized to treatment with *Avandia* 2 mg twice daily (n = 99) or metformin 500 mg twice daily (n = 101).(7,60) The study consisted of a 4-week single-blind, placebo run-in period including diet counseling, followed by a 24-week treatment period. Patients with fasting plasma glucose (FPG) levels > 126 mg/dL after a minimum of 8 weeks of treatment were increased to *Avandia* 4 mg twice daily or metformin 1000 mg twice daily. The primary efficacy endpoint was the change from baseline in HbA1c at 24 weeks. The secondary endpoint was a non-inferiority comparison of the change from baseline HbA1c at week 24 between treatment groups. Other tertiary endpoints included changes in FPG, C-peptide, and insulin levels from baseline in both treatment groups, and the treatment response rate for both groups at the end of 24 weeks. Pharmacokinetic parameters were also evaluated.

Baseline characteristics were similar between groups.(60)FPG decreased in patients naïve to diabetes medication (n = 104) and increased in patients withdrawn from prior medication (usually metformin) (n = 90) during the run-in period.(7) After at least 8 weeks of treatment, 49% of *Avandia*-treated patients and 55% of metformin-treated patients had their dose doubled. For the overall intent-to-treat population, at week 24, the mean change from baseline in HbA1c was -0.14% with *Avandia* and -0.49% with metformin. There was an insufficient number of patients in this study to establish statistically whether these observed mean treatment effects were similar or different. Treatment effects differed for patients naïve to therapy with antidiabetic drugs and for patients previously treated with antidiabetic therapy. Results for previously-treated and drug- naïve patients with a baseline HbA1c > 6.5% are presented in Table 4.

Table 4. Change in FPG and HbA1c from Baseline at Week 24 in Pediatric Patients with Baseline HbA1c > 6.5%*[7]

	Drug-Naïve Patients		**Previously-Treated Patients**	
	Metformin	*Avandia*	Metformin	*Avandia*
N	40	45	43	32
FPG (mg/dL)				
Baseline (mean)	170	165	221	205
Change from baseline (mean)	-21	-11	-33	-5
Adjusted Treatment Difference† [*Avandia*-metformin (95% CI)]‡		8 (-15, 30)		21 (-9, 51)
% of patients with ≥30 mg/dL decrease from baseline	43%	27%	44%	28%
HbA1c (%)				
Baseline (mean)	8.3	8.2	8.8	8.5
Change from baseline (mean)	-0.7	-0.5	-0.4	0.1
Adjusted Treatment Difference† [*Avandia*-metformin (95% CI)]‡		0.2 (-0.6, 0.9)		0.5 (-0.2, 1.3)
% of patients with ≥0.7% decrease from baseline	63%	52%	54%	31%

*Last Observation Carried Forward; †Change from baseline means are least squares means adjusting for baseline HbA1c, gender, and region; ‡Positive values for the difference favor metformin.

CI = Confidence interval; FPG = Fasting plasma glucose.

Treatment differences depended on baseline BMI or weight such that the effects of *Avandia* and metformin appeared more closely comparable among heavier patients.[7]

The safety analysis included all randomized patients.[60] Adverse events (AEs) were reported in 59% of patients treated with metformin and 62% of patients treated with *Avandia.* The most commonly (≥ 5%) reported adverse events are shown in Table 5.

Table 5. Adverse Events Reported by ≥5% of Pediatric Patients Treated With *Avandia* or Metformin as Monotherapy[7,60]

	Avandia	**Metformin**
Preferred Term	n = 99	n = 101
	%	%
Headache	17.2	13.9
Influenza	7.1	5.9
Upper Respiratory Tract Infection	6.1	5.9
Cough	6.1	5
Hyperglycemia	8.1	6.9
Dizziness	5.1	2
Back Pain	5.1	1
Nausea	4	10.9
Hypoglycemia	4	5
Nasopharyngitis	3	11.9
Vomiting	3	8.9
Abdominal Pain	3	6.9
Pharyngolaryngeal pain	2	5
Diarrhea	1	12.9
Sinusitis	1	5
Dysmennorhea	0	6.9

There were few withdrawals due to adverse events in both groups (*Avandia* n = 6; metformin n = 7).[60] In this study, one case of diabetic ketoacidosis was reported in the metformin group.[7] In addition, three patients treated with *Avandia* had an FPG of ~300 mg/dL, 2+ ketonuria, and an elevated anion gap. The median weight gain was 2.8 kg with *Avandia* and 0.2 kg with metformin. Fifty-four percent of patients treated with *Avandia* and 32% of patients treated with metformin gained ≥ 2 kg. In addition, 33% of patients treated with *Avandia* and 7% of patients treated with metformin gained ≥ 5 kg. Small changes in serum lipid parameters were reported. Small decreases in hemoglobin and hematocrit have also been reported in pediatric patients treated with *Avandia*.

In the population pharmacokinetic analysis, which included 33 males and 66 females with ages ranging from 10 to 17 years (weights ranging from 35 to 178.3 kg), mean oral clearance (CL/F) and volume of distribution (V/F) of rosiglitazone were 3.15 L/hr and 13.5 L, respectively.[7] These estimates of CL/F and V/F were consistent with the typical parameter estimates from a prior adult population analysis.

Use of Avandia in Patients with Renal Dysfunction

Pharmacokinetic Studies

There are no clinically relevant differences in the pharmacokinetics of *Avandia* in patients with mild to severe renal impairment or in hemodialysis-dependent patients, compared to subjects with normal renal function. No dosage adjustment is required in renally impaired patients receiving *Avandia*. Since metformin is contraindicated in patients with renal impairment, co-administration of metformin with *Avandia* is contraindicated in these patients.

Chronic Renal Insufficiency

An open-label study in healthy subjects and chronic renal insufficiency patients evaluated the pharmacokinetics of *Avandia* following the administration of a single 8 mg dose. [61,62] The primary objectives of this study were to characterize the pharmacokinetics and safety of a single oral *Avandia* dose in patients with varying degrees of renal insufficiency. Study participants were stratified according to Cockroft-Gault estimates of creatinine clearance (CrCl) into four groups: normal, CrCl > 80 ml/min (n = 12); mild, CrCl 60 - 80 ml/min (n = 15); moderate, CrCl 30 – 59 ml/min (n = 18); and severe but not requiring dialysis, CrCl ≤ 29 ml/min (n = 12). Point estimates and associated 95% confidence intervals for pharmacokinetic parameters for each renally impaired group relative to the normal group were calculated. Results of this study are presented in Table 6.

Table 6. Mean (SD) Pharmacokinetic Parameters Following a Single Dose of *Avandia* 8 mg in Healthy Subjects and Chronic Renal Insufficiency Patients

	Renal Impairment			
	Normal **n = 12**	**Mild** **n = 15**	**Moderate** **n = 18**	**Severe** **n = 12**
Cmax (ng/mL)	461 (88)	454 (108)	475 (104)	359 (105)
$AUC_{0\text{-}inf}$ (ng·h/mL)	2838 (781)	3126 (1239)	3236 (1054)	2290 (589)
Unbound Cmax (ng/mL)*	0.716 (0.191)	0.727 (0.162)	0.739 (0.237)	0.810 (0.282)
Unbound $AUC_{0\text{-}inf}$(ng·h/mL)*	4.23 (1.56)	5.09 (2.32)	5.04 (2.42)	4.76 (1.66)
tmax (h)†	2.0 (1.0-6.0)	2.0 (1.0-4.0)	2.0 (0.5-4.0)	2.0 (1.5-4.0)
t½ (h)	4.1 (1.1)	4.5 (1.9)	4.5 (0.8)	4.1 (1.0)
fu (%)*	0.16 (0.03)	0.16 (0.02)	0.15 (0.02)	0.22 (0.06)

*n = 10 normal; n = 14 mild; n = 17 moderate, n = 9 severe; †tmax presented as median (range) values.

AUC = area under the curve; Cmax = maximum drug concentration; fu = fraction unbound; inf = infinity; tmax = time to maximum concentration; t½ = half life.

Total and unbound maximum plasma concentrations (Cmax) and total area under the curve (AUC) values were similar for patients with mild and moderate renal insufficiency when compared to patients with normal renal function. However, total AUC (point estimate ratio of geometric means 0.81; 95% CI 0.64, 1.04) and Cmax (point estimate ratio of geometric means 0.76; 95% CI 0.63, 0.92) values were approximately 20 to 25% lower in the severe group compared to the normal group. The mean fraction unbound (% fu) was increased by 38% in the severe impairment group compared to the normal renal function group, and this may account for the lower total concentrations observed in the severe group.

Unbound AUC values were higher (10 – 20%) in all three of the renally-impaired groups; however, the differences were not considered clinically significant due to large inter-subject variability (approximately 40%). No differences were observed in mean unbound Cmax, half-life (t½) and median time to maximum concentration (tmax) between any of the groups. The results of this study suggest that dose adjustments do not appear necessary when administering *Avandia* to patients with mild to severe renal impairment.

The most commonly reported adverse events were headache and nausea. The investigators state that the safety profile appeared to be similar for all groups. All adverse events were mild to moderate in intensity and no patients withdrew from the study due to an adverse event.

Clinical Information

The efficacy and safety of *Avandia* in type 2 diabetic patients with chronic renal failure (not on dialysis) was evaluated in a 26-week, randomized, double-blind, placebo-controlled trial.[(63)] Chronic renal failure was defined as CrCl (Cockcroft-Gault equation) ≤ 79 ml/min. Patients receiving insulin therapy and/or a sulfonylurea were randomized to *Avandia* 4 mg once daily (n = 148) or placebo (n = 143). Only a small number of randomized patients received *Avandia* plus a sulfonylurea or placebo plus a sulfonylurea, the majority received *Avandia* plus insulin alone or insulin plus a sulfonylurea (n = 112) or placebo plus insulin alone or insulin plus a sulfonylurea (n = 109).[(63)] The dose of insulin and sulfonylurea remained constant during the study unless hypoglycemia was reported. If hypoglycemia occurred the dose of insulin or the sulfonylurea was adjusted. After 8-12 weeks, if fasting plasma glucose (FPG) remained > 110 mg/dl the dose of *Avandia* was increased to 4 mg twice daily. The primary efficacy endpoint was mean change in HbA1c from baseline to week 26.

The demographics of the two groups were similar at baseline.[(63)] The majority of patients were white (98%) and male (61%) with a mean age of 66 years and a mean duration of diabetes of 14.6 years. Forty-eight percent of patients had moderate renal failure (CrCl 60-79 ml/min), 32.3% and 16.7% had mild renal failure (CrCl 30-59 mL/min) and severe renal failure (CrCl ≤ 29 ml/min), respectively. At baseline, 69% of patients were on insulin monotherapy, 24.4% were on sulfonylurea monotherapy, and 6.5% were on the combination of insulin and sulfonylurea therapy. Ten patients received triple therapy with *Avandia*, insulin, and a sulfonylurea.

Avandia 4 or 8 mg/day in combination with insulin alone or insulin plus a sulfonylurea (n = 112) improved HbA1c and FPG values from baseline compared with placebo plus insulin alone or insulin plus a sulfonylurea (n = 109).[63] The HbA1c results were similar regardless of renal function at baseline. FPG decreased in all groups, however the difference was statistically significant only in the moderate renal function group.

Many of the patients enrolled in the study had a history of significant cardiovascular disease and combined with their decreased renal function and long-standing diabetes were at an increased risk for further cardiovascular and fluid-related events.[63] At baseline, 6.3% (7/112) of patients treated with *Avandia* plus insulin alone or insulin plus a sulfonylurea had a history of heart failure compared to 4.6% (5/109) treated with insulin alone or insulin plus a sulfonylurea. In this study, the incidence of cardiovascular events was similar between the treatment groups regardless of the degree of renal impairment.

The rate of edema-related (edema, edema dependent, edema generalized, edema legs, and edema peripheral) adverse events was 22.3% with *Avandia* plus insulin alone or insulin plus a sulfonylurea compared to 11.0% on insulin alone or insulin plus a sulfonylurea.[63] When the incidence of edema was evaluated by severity of renal function for patients on *Avandia* plus insulin alone or insulin plus a sulfonylurea, the incidence of edema related events was similar to that seen in the total population regardless of renal function. In the mild impairment group, the rate of edema-related events was similar with both *Avandia* plus insulin and/or a sulfonylurea (21.9%) and insulin and/or a sulfonylurea (20.0%).

Hypoglycemia occurred more frequently with *Avandia* therapy, 27.7% with *Avandia* plus insulin alone or insulin plus a sulfonylurea compared to 15.6% with insulin alone or insulin plus a sulfonylurea.[63] The incidence of hypoglycemia was higher with *Avandia* in both the mild and moderate renal impairment groups. In the severe renal function group, the rates of hypoglycemia were the same in both treatment groups.

The rate of withdrawal from the study due to adverse events was similar with *Avandia* plus insulin alone or insulin plus a sulfonylurea (13 patients) and insulin alone or insulin plus a sulfonylurea (9 patients).[63] Withdrawals due to adverse events in both groups were more frequent in patients taking insulin and in patients with more severe renal dysfunction at baseline.

4.7 Pharmacology

General

Refer to Enclosed Prescribing Information.

4.8 Pharmacokinetics/Pharmacodynamics

Refer to Enclosed Prescribing Information.

4.9 Contraindications

Refer to Enclosed Prescribing Information.

4.10 Warnings/Precautions

WARNING: CONGESTIVE HEART FAILURE AND MYOCARDIAL ISCHEMIA

- **Thiazolidinediones, including rosiglitazone, cause or exacerbate congestive heart failure in some patients. After initiation of *Avandia*, and after dose increases, observe patients carefully for signs and symptoms of heart failure (including excessive, rapid weight gain, dyspnea, and/or edema). If these signs and symptoms develop, the heart failure should be managed according to current standards of care. Furthermore, discontinuation or dose reduction of *Avandia* must be considered.**
- ***Avandia* is not recommended in patients with symptomatic heart failure. Initiation of *Avandia* in patients with established NYHA Class III or IV heart failure is contraindicated.**
- **A meta-analysis of 42 clinical studies (mean duration 6 months; 14,237 total patients), most of which compared *Avandia* to placebo, showed *Avandia* to be associated with an increased risk of myocardial ischemic events such as angina or myocardial infarction. Three other studies (mean duration 41 months; 14,067 total patients), comparing *Avandia* to some other approved oral**

antidiabetic agents or placebo, have not confirmed or excluded this risk. In their entirety, the available data on the risk of myocardial ischemia are inconclusive.

Refer to Enclosed Prescribing Information.

4.11 Adverse Events

General

Refer to Enclosed Prescribing Information.

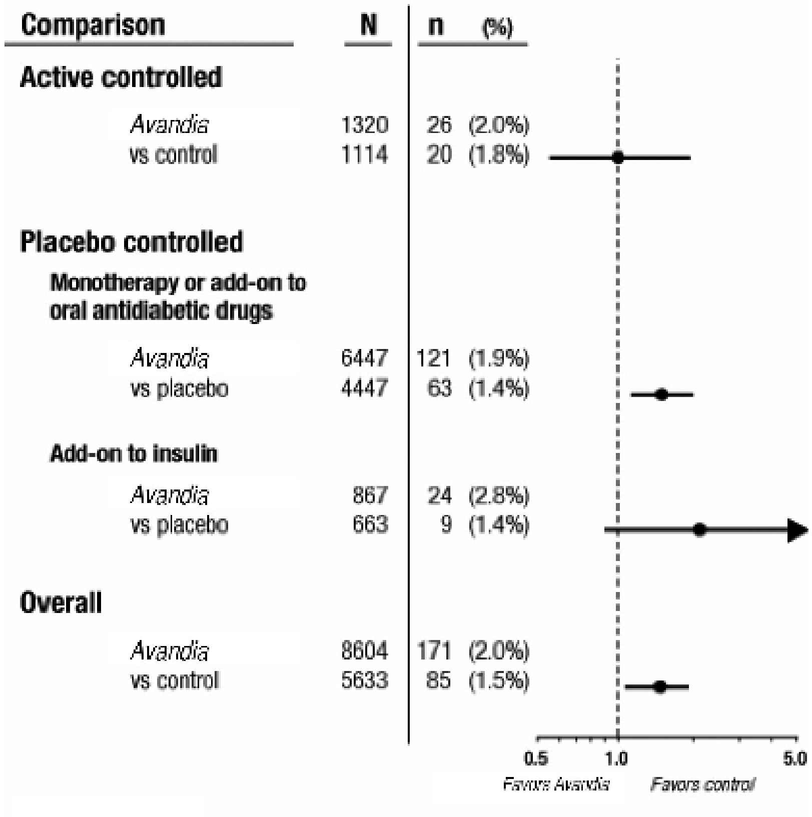
The Risk of Myocardial Ischemic Events in Patients Treated with Avandia

FDA Meta-Analysis of Myocardial Ischemia in a Group of 42 Clinical Trials(7)

A meta-analysis was conducted retrospectively to assess cardiovascular adverse events reported across 42 double-blind, randomized, controlled clinical trials (mean duration 6 months).(64) These studies had been conducted to assess glucose-lowering efficacy in type 2 diabetes, and prospectively planned adjudication of cardiovascular events had not occurred in the trials. Some trials were placebo-controlled and some used active oral antidiabetic drugs as controls. Placebo-controlled studies included monotherapy trials (*Avandia* monotherapy versus placebo monotherapy) and add-on trials (*Avandia* or placebo, added to sulfonylurea, metformin, or insulin). Active control studies included monotherapy trials (*Avandia* monotherapy versus sulfonylurea or metformin monotherapy) and add-on trials (*Avandia* plus sulfonylurea or *Avandia* plus metformin, versus sulfonylurea plus metformin). A total of 14,237 patients were included (8,604 in treatment groups containing *Avandia*, 5,633 in comparator groups), with 4,143 patient-years of exposure to *Avandia* and 2,675 patient-years of exposure to comparator. Myocardial ischemic events included angina pectoris, angina pectoris aggravated, unstable angina, cardiac arrest, chest pain, coronary artery occlusion, dyspnea, myocardial infarction, coronary thrombosis, myocardial ischemia, coronary artery disease, and coronary artery disorder. In this analysis, an increased risk of myocardial ischemia with *Avandia* versus pooled comparators was observed (2% *Avandia* versus 1.5% comparators, odds ratio [OR] 1.4, 95% confidence interval [CI] 1.1, 1.8). An increased risk of myocardial ischemic events with *Avandia* was observed in the placebo-controlled studies, but not in the active-controlled studies. (See Figure 1) A greater increased risk of myocardial ischemic events was observed in studies where *Avandia* was added to insulin (2.8% for *Avandia* plus insulin versus 1.4% for placebo plus insulin, [OR 2.1, 95% CI 0.9, 5.1]). This increased risk reflects a difference of 3 events per 100 patient years (95% CI -0.1, 6.3) between treatment groups.

In studies in which *Avandia* was added to insulin, *Avandia* increased the risk of congestive heart failure and myocardial ischemia.(7) Coadministration of *Avandia* and insulin is not recommended. In five, 26-week, controlled, randomized, double-blind trials which were included in the meta-analysis, patients with type 2 diabetes mellitus were randomized to coadministration of *Avandia* and insulin (N = 867) or insulin (N = 663). In these 5 trials, *Avandia* was added to insulin. These trials included patients with long-standing diabetes (median duration of 12 years) and a high prevalence of pre-existing medical conditions, including peripheral neuropathy, retinopathy, ischemic heart disease, vascular disease, and congestive heart failure. The total number of patients with emergent congestive heart failure was 21 (2.4%) and 7 (1.1%) in the *Avandia* plus insulin and insulin groups, respectively. The total number of patients with emergent myocardial ischemia was 24 (2.8%) and 9 (1.4%) in the *Avandia* plus insulin and insulin groups, respectively (OR 2.1 [95% CI 0.9, 5.1]). Although the event rate for congestive heart failure and myocardial ischemia was low in the studied population, consistently the event rate was 2-fold or higher with coadministration of *Avandia* and insulin. These cardiovascular events were noted at both the 4 mg and 8 mg daily doses of *Avandia*.

Figure 1. Forest Plot of Odds Ratios (95% Confidence Intervals) for Myocardial Ischemic Events in the Meta-Analysis of 42 Clinical Trials



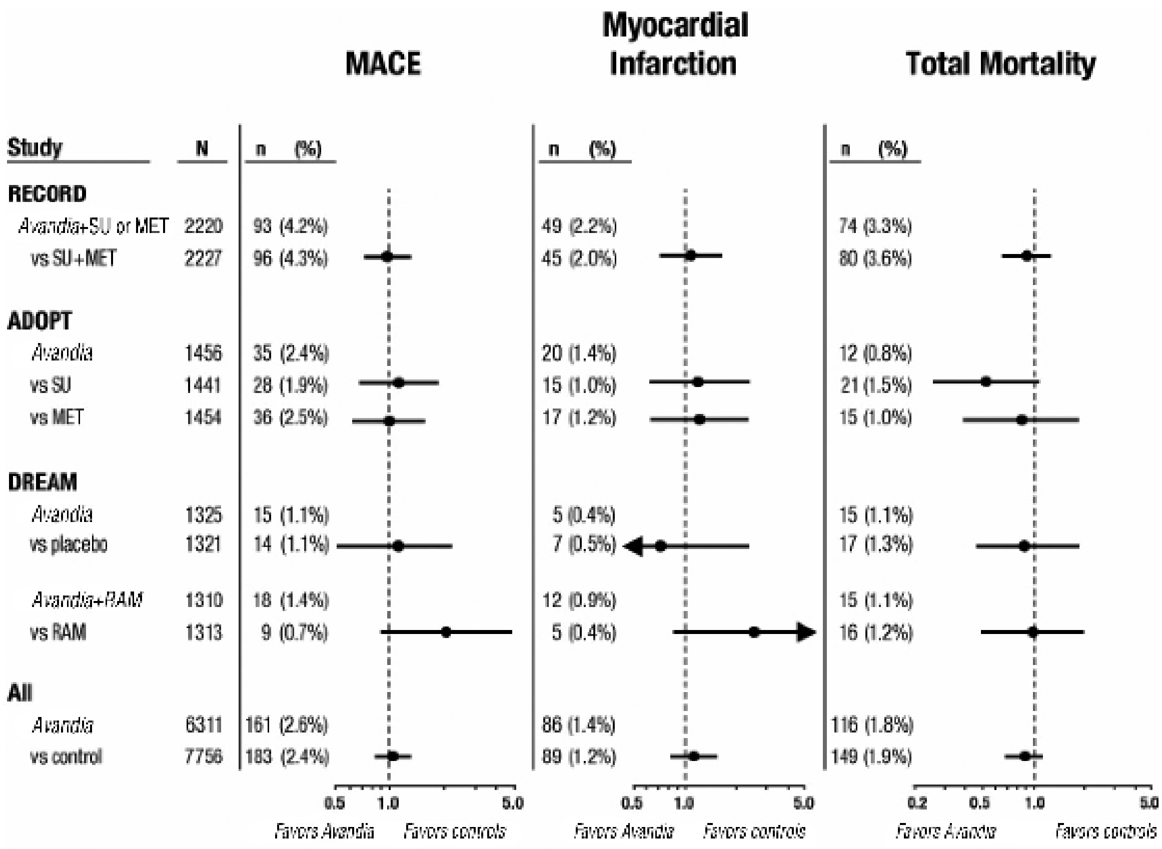
A greater increased risk of myocardial ischemia was also observed in patients who received *Avandia* and background nitrate therapy. For *Avandia* (N = 361) versus control (N = 244) in nitrate users, the odds ratio was 2.9 (95% CI 1.4, 5.9), while for non-nitrate users (about 14,000 patients total), the odds ratio was 1.3 (95% CI 0.9, 1.7). This increased risk represents a difference of 12 myocardial ischemic events per 100 patient years (95% CI 3.3, 21.4). Most of the nitrate users had established coronary heart disease. Among patients with known coronary heart disease who were not on nitrate therapy, an increased risk of myocardial ischemic events for *Avandia* versus comparator was not demonstrated. Use of *Avandia* with nitrates is not recommended.

Myocardial Ischemic Events in Large Long-Term Prospective Randomized Controlled Trials of *Avandia*[7]

Data from 3 other large long-term prospective randomized controlled clinical trials of *Avandia* were assessed separately from the meta-analysis. These 3 trials include a total of 14,067 patients (treatment groups containing *Avandia* N = 6,311, comparator groups N = 7,756), with patient-year exposure of 21,803 patient-years for *Avandia* and 25,998 patient-years for comparator. Duration of follow-up exceeded 3 years in each study. ADOPT (A Diabetes Outcomes Progression Trial) was a 4- to 6-year randomized, active-controlled study in recently diagnosed patients with type 2 diabetes naïve to drug therapy.[8] It was an efficacy and general safety trial that was designed to examine the durability of *Avandia* as monotherapy (N = 1,456) for glycemic control in type 2 diabetes, with comparator arms of sulfonylurea monotherapy (N = 1,441) and metformin monotherapy (N = 1,454). DREAM (Diabetes Reduction Assessment with Rosiglitazone and Ramipril Medication) was a 3- to 5-year randomized, placebo-controlled study in patients with impaired glucose tolerance and/or impaired fasting glucose.[65] It had a 2x2 factorial design, intended to evaluate the effect of *Avandia*, and separately of ramipril (an angiotensin converting enzyme inhibitor [ACEI]), on progression to overt diabetes. In DREAM, 2,635 patients were in treatment groups containing *Avandia*, and 2,634 were in treatment groups not containing *Avandia*. Interim results have been published for RECORD (Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of

Glycemia in Diabetes), an ongoing open-label, 6-year cardiovascular outcomes study in patients with type 2 diabetes with an average treatment duration of 3.75 years.[14] RECORD includes patients who have failed metformin or sulfonylurea monotherapy; those who have failed metformin are randomized to receive either add-on *Avandia* or add-on sulfonylurea, and those who have failed sulfonylurea are randomized to receive either add-on *Avandia* or add-on metformin. In RECORD, a total of 2,220 patients are receiving add-on *Avandia*, and 2,227 patients are on one of the add-on regimens not containing *Avandia*. For these 3 trials, analyses were performed using a composite of major adverse cardiovascular events (cardiovascular death, myocardial infarction, and stroke), referred to hereafter as MACE. This endpoint differed from the meta-analysis's broad endpoint of myocardial ischemic events, more than half of which were angina. Myocardial infarction included adjudicated fatal and nonfatal myocardial infarction plus sudden death. As shown in Figure 2, the results for the three endpoints (MACE, MI, and Total Mortality) were not statistically significantly different between *Avandia* and comparators.

Figure 2. Hazard Ratios for the Risk of MACE (Myocardial Infarction, Cardiovascular Death, or Stroke), Myocardial Infarction, and Total Mortality With Avandia Compared With a Control Group



SU = sulfonylurea; MET = metformin; RAM = ramipril

In preliminary analyses of the DREAM trial, the incidence of cardiovascular events was higher among subjects who received *Avandia* in combination with ramipril than among subjects who received ramipril alone, as illustrated in Figure 2. This finding was not confirmed in ADOPT and RECORD (active-controlled trials in patients with diabetes) in which 30% and 40% of patients respectively, reported ACE-inhibitor use at baseline.

In their entirety, the available data on the risk of myocardial ischemia are inconclusive. Definitive conclusions regarding this risk await completion of an adequately-designed cardiovascular outcome study. There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with *Avandia* or any other oral antidiabetic drug.

Reports of Fluid Related Events with Avandia

Clinical Information

Edema

Avandia should be used with caution in patients with edema.[7] In controlled clinical trials of patients with type 2 diabetes, mild to moderate edema was reported in patients treated with *Avandia* (Table 7). The event usually did not require discontinuation of treatment with *Avandia* and tended to be reported more frequently at higher doses. Patients with ongoing edema are more likely to have adverse events associated with edema if started on combination therapy with insulin and *Avandia*. Coadministration of *Avandia* and insulin is not recommended.

Table 7. Incidence of Edema with *Avandia* in Controlled Clinical Trials of Type 2 Diabetes Patients

Treatment Group	N	%
Avandia monotherapy[7]*	2526	4.8
Avandia 4 or 8 mg/day + metformin[66]†	338	4.4
Avandia 8 mg/day + sulfonylurea[7]	885	12.4
Avandia 4 or 8 mg/day + metformin + sulfonylurea[67]	561	12.1
Avandia + insulin[7]‡	408	14.7
Placebo[7]	601	1.3
Metformin[7]	225	2.2
Sulfonylurea[7]	626	1.0
Metformin + sulfonylurea[67]	276	4.0
Insulin[7]	203	5.4

*Includes all doses studied, majority of patients received *Avandia* 4 or 8 mg/day. †*Avandia* added to maximum doses of metformin. ‡Includes patients on *Avandia* 4 or 8 mg/day. Coadministration of *Avandia* and insulin is not recommended.

Congestive Heart Failure (CHF)

Avandia, like other thiazolidinediones, alone or in combination with other antidiabetic agents, can cause fluid retention, which may exacerbate or lead to heart failure.[7] Patients should be observed for signs and symptoms of heart failure. If these signs and symptoms develop, the heart failure should be managed according to current standards of care. Furthermore, discontinuation or dose reduction of *Avandia* must be considered. *Avandia* is not recommended in patients with symptomatic heart failure. Initiation of *Avandia* in patients with established NYHA Class III and IV heart failure is contraindicated.

In five, 26-week, controlled, randomized, double-blind trials, patients with type 2 diabetes were randomized to coadministration of *Avandia* and insulin (N = 867) or insulin (N = 663).[7] In these 5 trials, *Avandia* was added to insulin. These trials included patients with long-standing diabetes (median duration of 12 years) and a high prevalence of pre-existing medical conditions, including peripheral neuropathy, retinopathy, ischemic heart failure, vascular disease, and congestive heart failure. The total number of patients with emergent CHF was 21 (2.4%) and 7 (1.1%) in the *Avandia* plus insulin and insulin groups, respectively. These cardiovascular events were noted at both the 4 mg and 8 mg daily doses of *Avandia*. Coadministration of *Avandia* and insulin is not recommended.

Reports of CHF from an integrated clinical trials analysis (ICT), DREAM, ADOPT, and RECORD interim analysis remain consistent with previous reports and observations from individual and pooled controlled clinical trials of an increased incidence of CHF in patients treated with *Avandia*.[8,65,14,10]

***Avandia* vs. Placebo in Type 2 Diabetes Patients with NYHA Class I or II CHF**

A 52-week, double-blind, placebo-controlled, non-inferiority echocardiographic study was conducted in 224 patients with type 2 diabetes and NYHA Class I or II CHF.[68] Patients with an ejection fraction ≤ 45% treated with angiotensin converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs) and/or diuretics at study entry were randomized to *Avandia* (4 mg/day increased to 8 mg/day) or placebo in addition to background antidiabetic therapy. Background antidiabetic therapy included diet, exercise and/or oral monotherapy or oral combination therapy of no more than 2 medications (insulin therapy was excluded at entry to the study and was not permitted during the study except during acute episodes such as hospitalization, trauma, or infection to manage glycemic control). [68]The dose and regimen of oral antidiabetic therapy could be changed to achieve glycemic control. However, initiation or uptitration of metformin was not permitted during the study due to the risk of lactic acidosis. If a patient experienced signs or symptoms of fluid-retention or an exacerbation of CHF, CHF medications could be adjusted by optimizing diuretic therapies, adjusting background ACEI/ARB therapy, adding cardiac glycosides, or the dose of *Avandia* could be reduced.

An independent committee conducted a blinded evaluation of fluid-related events (including CHF) and cardiovascular hospitalizations according to predefined criteria (adjudication).[68] Separate from the adjudication, other cardiovascular adverse events were reported by investigators. Although no treatment difference in change from baseline of ejection fractions was observed, more cardiovascular adverse events were observed with *Avandia* compared to placebo during the 52-week study (Table 8Table 41).

Table 8. Emergent Cardiovascular Adverse Events (Study 211)[68]Table 41. Emergent Cardiovascular Adverse Events (Study 211)[68]

	Avandia	Placebo	P-value
EVENTS	N = 110 n (%)	N = 114 n (%)	
Major Adjudicated Clinical Endpoints			
Cardiovascular Death	5 (4.8)	4 (3.8)	0.85
All-cause Mortality	8 (7.7)	5 (4.8)	0.48
All-cause Mortality or Worsening CHF	11 (10.6)	8 (7.5)	0.59
Other Adjudicated Clinical Endpoints			
Cardiovascular Hospitalization*	21 (19.1)	15 (13.2)	0.47
Definite Worsening CHF	5 (4.5)	4 (3.5)	0.86
Possible Worsening CHF	2 (1.8)	0	N/A †
New or Worsening Edema	28 (25.5)	10 (8.8)	0.01
New or Worsening Dyspnea	29 (26.4)	19 (16.7)	0.20
Increase in CHF Medication	36 (32.7)	20 (17.5)	0.04
* Major reasons for cardiovascular hospitalization included worsening of CHF, myocardial infarction, and stroke/transient ischemic attack † No events occurred in one treatment group, preventing analysis using this model			

Weight Gain with Avandia Monotherapy

Pivotal Clinical Trials Data

Dose-related weight gain has been seen with *Avandia* alone and in combination with other hypoglycemic agents. The mechanism of weight gain is unclear but probably involves a combination of fluid retention and fat accumulation.

Table 9. Weight Changes (kg) from Baseline During Clinical Trials with *Avandia* as Monotherapy[48,49,50]

Regimen		**Control Group**		***Avandia*** **4 mg/day**	***Avandia*** **8 mg/day**
Monotherapy	Duration		Median (25th, 75th percentile)	Median (25th, 75th percentile)	Median (25th, 75th Percentile)
	26 weeks	Placebo	-0.9 (-2.8, 0.9) n = 210	1.0 (-0.9, 3.6) n = 436	3.1 (1.1, 5.8) n = 439
	52 weeks	Sulfonylurea	2.0 (0, 4.0) n = 173	2.0 (-0.6, 4.0) n = 150	2.6 (0, 5.3) n = 157

Additional Studies

In a 4- to 6-year, monotherapy, comparative trial (ADOPT) in patients recently diagnosed with type 2 diabetes not previously treated with antidiabetic medication, the mean change in weight observed was +

1.5 lbs/yr (+ 0.7 kg/yr), - 0.7 lbs/yr (- 0.3 kg/yr), and - 0.4 lbs/yr (- 0.2 kg/yr) with *Avandia*, metformin, and glyburide, respectively, based on mean values using a repeated measures model beginning at 6 months.(8)

A 24-week, randomized, double-blind, multicenter, parallel-group study evaluated the efficacy and safety of *Avandia* in poorly-controlled, drug naïve patients with type 2 diabetes (baseline HbA1c ≥10%).(69) Eligible patients were randomized to receive either *Avandia* 4 mg once daily or *Avandia* 8 mg once daily. The mean change in weight at the end of the study was +1.8 kg and + 3.6 kg in the *Avandia* 4 mg/day (n = 44) and 8 mg/day (n = 52) groups, respectively.

A 16-week randomized, double-blind, placebo-controlled study (n = 33) found that *Avandia* appears to promote fat deposition in subcutaneous adipose tissue rather that intra-abdominal (visceral) fat regions and may also reduce levels of intra-hepatic fat in patients with type 2 diabetes. (70) Similarly, in a 4-month study comparing *Avandia* 8 mg/day (n = 11) and metformin 2000 mg/day (n = 12) in obese patients with type 2 diabetes, *Avandia* 8 mg/day was shown to result in a 1.1 kg increase in weight with a reduction in visceral fat by approximately 10% (-27 ± 13 cm^2). (71) Metformin resulted in a 2.7 kg weight loss but there was no change in visceral fat. Please note, abstracts are frequently based on early analyses and much of the information on study design and actual data have not been presented.

Post-marketing Surveillance Data

In postmarketing experience, there have been reports of unusually rapid increases in weight and increases in excess of that generally observed in clinical trials.(7) Patients who experience such increases should be assessed for fluid accumulation and volume-related events such as excessive edema and congestive heart failure.

Reports of Macular Edema with Avandia

Post-marketing reports of new-onset or worsening diabetic macular edema with decreased visual acuity have been reported with *Avandia*. Many of these patients reported concurrent peripheral edema. In some cases, the visual events resolved or improved following discontinuation of the drug.

Background

Macular edema typically occurs in association with diabetic retinopathy, although it is more likely to occur as retinopathy progresses. (72) Diabetic macular edema is a swelling of the retina that occurs after breakdown of the blood-retinal barrier because of leakage of dilated hyperpermeable capillaries and microaneurysms within the macula (the central portion of the retina. (73) Risk factors for macular edema include duration of diabetes, presence of retinopathy, hypertension, and poor glycemic control. (72) (73)

Clinical Data

In a retrospective chart review, Ryan et al identified 30 type 2 diabetic patients using a TZD who had both lower extremity edema that increased since starting the TZD and clinically significant macular edema.(74) Eleven patients received *Avandia*, 17 patients received Actos® (pioglitazone hydrochloride), and 2 patients received both TZDs at different times. Clinically significant macular edema was documented by clinical examination as well as review of color photographs and fluorescein angiograms. Fluid retention was noted to be present or absent. Response to TZD cessation was measured by reported weight loss, clinical estimation of lower extremity edema, visual acuity changes, and change in macular edema. Therapeutic ocular intervention included focal laser treatment and therapeutic systemic intervention included TZD cessation, diuresis, and dialysis (1 case).

Of the 30 type 2 diabetes patients (average duration since diagnosis: 8.3 years), 23 patients also had hypertension, 6 patients had heart failure, and 1 patient had renal failure. (74) Additionally, 2 patients were on TZD monotherapy, 12 patients were receiving other oral antidiabetic medications with the TZD, 7 patients were receiving insulin in combination with the TZD, 7 patients were receiving other oral antidiabetic medications and insulin with the TZD, and 2 patients had no information available. Clinically significant macular edema was bilateral in 24 patients and unilateral in 6 patients. Macular laser photocoagulation was performed on 26 patients (48/60 eyes; ≥ 2 times in 22/60 eyes). Fluorescein angiography and clinical evaluation by a physician determined that the macular edema was diffuse in at least 1 eye of 19/30 patients, with 17/30 patients having bilateral diffuse macular edema. Average patient-reported weight gain while on the TZD was 23 lbs. Average patient-reported weight loss following TZD cessation was 19 lbs.

Decreased lower extremity edema was observed in all 11 patients followed for > 3 months after TZD cessation. [74] Ten of 11 patients also reported weight loss after TZD cessation. In these 11 patients, the average patient-reported weight gain was 30 lbs (range, 15-50 lbs) while on the TZD. The average patient-reported weight loss was 19 lbs (range 0-30 lbs) following TZD cessation. Of these 11 patients, 10 had hypertension, 3 developed renal failure, and 3 had heart failure. Reduction in macular edema occurred in < 3 months in 4/11 patients and in 8/11 patients over a 1- to 2-year period. These results should be interpreted with caution due to the retrospective nature of the analysis and the limitations inherent in such an analysis.

GlaxoSmithKline vigilantly monitors the safety of all of its products. As part of this monitoring, postmarketing reports of new onset or worsening (diabetic) macular edema have been received for some diabetic patients taking rosiglitazone or another thiazolidinedione (TZD). Some patients presented with blurred vision or decreased visual acuity, but some patients appear to have been diagnosed on routine ophthalmologic examination. Most patients had peripheral edema at the time macular edema was diagnosed. Some patients had improvement in their macular edema after discontinuation of their TZD. Patients with diabetes should have regular eye exams by an ophthalmologist, per the Standards of Care of the American Diabetes Association. Additionally, any diabetic patient who reports any kind of visual symptom should be promptly referred to an ophthalmologist, regardless of the patient's underlying medications or other physical findings[7].

Avandia and Fractures

Background

Over the last 20 years, data has been reported that indicates patients with type 2 diabetes are at increased risk of nonvertebral fracture, particularly fractures of the hip, arm and foot.[75,76,77,78] Elderly diabetic women are up to 6 times more likely to have a hip fracture than elderly nondiabetic women; the corresponding figure for elderly diabetic men is even higher (up to 8-fold higher risk).[79] The reason for this is unclear, particularly since type 2 diabetes tends to be associated with above average bone density and thus might be expected to be protective against osteoporosis and fracture.[78] Type 2 diabetes is known to be a predisposing factor for disability and falls in the elderly, and this predisposition has been postulated to account for some of the fractures.[80,81] However, even after adjusting for the frequency of falls, the fracture risk for diabetic patients persists.[78] Further information regarding fracture risk in type 2 diabetes is provided by analysis of data from the Women's Health Initiative Observational Study (WHIOS). [78] The WHIOS study enrolled a racially diverse group of over 93,000 postmenopausal women, collected detailed information on risk factors for fracture, and followed up this population for incident falls and fractures. A separate analysis of fracture data at various skeletal sites was conducted among the subgroup of 5,285 postmenopausal females (age 50-79 years; mean 64.9 years) with type 2 diabetes who participated in this study. Information on antidiabetic drug use in this patient population was limited to insulin, which was being taken by 17% of patients on study entry. Over the 7 year follow-up period, women with diabetes were 29% more likely to have a fracture of any type than women without diabetes.

Clinical Information

The ADOPT (A Diabetes Outcome Progression Trial) trial was designed to measure the long-term durability of glycemic control in people recently diagnosed with type 2 diabetes (≤3 years) receiving monotherapy with *Avandia* versus metformin or glyburide.[8] Among the 4,351 people with type 2 diabetes involved in ADOPT and treated for a median of 4 years, 200 people reported to experience at least one bone fracture event: 92 in the *Avandia* group (6.3% or 1.86 per 100 patient years); 59 in the metformin group (4.1% or 1.20 per 100 patient years) and 49 in the glyburide group (3.4% or 1.15 per 100 patient years).[82] The estimated hazard ratios [with 95% confidence interval (CI)] for the risk of fracture with *Avandia* versus metformin and glyburide were 1.57 (1.13, 2.17; $P = 0.0073$) and 1.61 (1.14, 2.28; $P = 0.0069$), respectively.

Men and women randomized to the three treatment groups were well matched at baseline.[82] The majority of women in the study were >50 years old (71%) and postmenopausal (77%) by self report. Please refer to Table 10. There were no clear differences in the pattern of use of concomitant medications, estrogen containing hormones, calcium supplements, bisphosphonates, thiazide and loop diuretics, or glucocorticoids, between women who did and did not report fracture within any treatment group.

Table 10. Fracture Rates Reported in Women by Menopausal Status and Age[82]

	Avandia			**Metformin**			**Glyburide**		
Pre-menopausal n† (%)	10/147 (6.8)			4/127 (3.2)			3/156 (1.9)*		
Post-menopausal n‡ (%)	50/498 (10.0)			26/463 (5.6)*			18/449 (4.0)*		
	With Fracture N = 60	Without Fracture N = 585	*P* Value	With Fracture N = 30	Without Fracture N = 560	*P* Value	With Fracture N = 21	Without Fracture N = 584	*P* Value
Age ≤ 50 n (%)	11 (18.3)	181 (30.9)	0.065	8 (26.7)	153 (27.3)	0.954	3 (14.3)	176 (30.1)	0.012
Age > 50 - ≤ 60 n (%)	24 (40.0)	205 (35.0)		11 (36.7)	203 (36.3)		5 (23.8)	197 (33.7)	
Age > 60 n (%)	25 (41.7)	199 (34.0)		11 (36.7)	204 (36.4)		13 (61.9)	211 (36.1)	

*$P < 0.05$ vs. *Avandia*; † n = number of premenopausal women that reported a fracture/total number of premenopausal women; ‡ n = number of postmenopausal women that reported a fracture/total number of postmenopausal women.

Of the 1,840 women in ADOPT, 111 experienced at least one bone fracture event, predominantly in the upper and lower limb.[82] These sites of fracture are different from those usually associated with postmenopausal osteoporosis (e.g., hip or spine). Of these, 60 women were in the *Avandia* group (9.3% or 2.74 per 100 patient years); 30 were in the metformin group (5.1% or 1.54 per 100 patient years) and 21 were in the glyburide group (3.5% or 1.29 per 100 patient years). The hazard ratios (with 95% CI) for the risk of fracture with *Avandia* versus metformin and glyburide in women were 1.81 (1.17, 2.80; $P = 0.008$) and 2.13 (1.30, 3.51; $P = 0.0029$), respectively. There was no increased risk of fracture with *Avandia* over the first 12 months of treatment, the increased risk manifested beyond 12 months of exposure. Amongst women that experienced a fracture event, 11.7%, 16.7%, and 23.8% reported accidental limb injury or fall within 30 days prior to the fracture and 18.3%, 16.7%, 14.3% reported more than one fracture in the *Avandia*, metformin, and glyburide groups, respectively. Please refer to Table 11. The observed fracture rates from ADOPT appear to be within the range seen in a literature based review of observational studies in women with diabetes and upon analysis of large managed care databases. [75,78,83,84]

There were no statistically significant differences observed among treatment groups in ADOPT in the number of fractures reported in men.[82] The hazard ratios for the risk of fracture with *Avandia* versus metformin and glyburide in men were 1.18 (0.72, 1.96; $P = 0.5115$) and 1.08 (0.65, 1.79; $P = 0.7680$), respectively.

Table 11. Patients with Fractures in ADOPT[82]

	Avandia		Metformin		Glyburide	
MALE PATIENTS	811 Males		864 Males		836 Males	
	n (%)	Rate/100 PY	n (%)	Rate/100 PY	n (%)	Rate/100 PY
Experienced a fracture	32 (4.0)	1.16	29 (3.4)	0.98	28 (3.4)	1.07
FEMALE PATIENTS	645 Females		590 Females		605 Females	
	n (%)	Rate/100 PY	n (%)	Rate/100 PY	n (%)	Rate/100 PY
Experienced a fracture*	60 (9.3)	2.74	30 (5.1)	1.54	21 (3.5)	1.29
Lower limb†	36 (5.58)	1.65	18 (3.05)§	0.92	8 (1.32)§	0.49
Hip	2 (0.31)	0.09	2 (0.34)	0.1	0	0
Foot	22 (3.41)	1.01	7 (1.19)§	0.36	4 (0.66)§	0.25
Upper limb‡	22 (3.41)	1.01	10 (1.70)	0.51	9 (1.49)	0.55
Hand	8 (1.24)	0.37	4 (0.68)	0.21	1 (0.17)	0.06
Humerus	5 (0.78)	0.23	0	0	0	0
Wrist	5 (0.78)	0.23	3 (0.51)	0.15	4 (0.66)	0.25
Spine	1 (0.16)	0.05	1 (0.17)	0.05	1 (0.17)	0.06

* Some patients experienced fractures in more than one category; †Other sites of fracture included: ankle, femur, fibula, lower limb (general), patella, and tibia; ‡Other sites of fracture included: clavicle, forearm, radius, and upper limb (general).

n = number of patients; Rate/100 PY = Patients with events per 100 patient years.

§ $P < 0.05$ vs. *Avandia*

An independent safety committee reviewed an interim analysis of fractures in another large ongoing, long-term, controlled rosiglitazone clinical trial. The primary purpose of that study is to investigate cardiovascular endpoints in patients with type 2 diabetes mellitus. The results of the preliminary analysis were reported to GlaxoSmithKline as being consistent with the observations from ADOPT. The independent safety committee also recommended that the study continue without modification. Final results of this study are anticipated to be available in 2009.

Long-term use of thiazolidinediones and fractures in type 2 diabetes: a meta-analysis

Loke and colleagues assessed the risk of fractures in patients with impaired glucose tolerance (IGT) or type 2 diabetes with the long-term (≥ 1 year) use of thiazolidinediones (TZDs).[85] This analysis evaluated 10 randomized controlled trials (N = 13,715) and 2 observational studies (N = 31,679) through June 2008 that described the risk of fracture or change in bone density with TZDs. Long-term randomized controlled trials and observational studies that described the risk of fracture with any TZD (*Avandia*, pioglitazone, or troglitazone) were included in the analysis. The secondary outcome evaluated the effects of TZD therapy on bone mineral density (BMD). In this analysis, randomized controlled trials and observational studies of any duration that compared changes in bone mineral density in patients with and without TZD exposure were evaluated.

Pooled data from the 10 randomized controlled trials evaluated the risk of fractures associated with TZD therapy. As compared to the control, TZD therapy significantly increased the risk of overall fractures, (Odds Ratio[OR] 1.45, 95% Confidence Interval [CI] 1.18-1.79; $P < 0.001$) Additionally, data from 5 randomized trials reported that TZD therapy significantly increased the risk of fracture among women compared to control (OR 2.23, 95% CI 1.65-3.01; $P < 0.001$). Therapy with TZDs did not increase the risk of fracture risk among men (OR 1.00, 95% CI 0.73-1.39; $P = 0.98$).

A correlation between TZD exposure and fractures was also reported in 2 observational studies. A case-controlled study demonstrated a significant association between TZD exposure (current users with > eight prescriptions) and fractures among women (OR 2.56, 95% CI 1.43-4.58). Additionally, a separate cohort study reported that *Avandia* was significantly associated with fractures when compared to women taking metformin (OR 1.38, 95% CI 1.03-1.82). However, no greater fracture risk was seen in the comparison of *Avandia* and sulfonylurea (OR 0.89, 95% CI 0.69-1.14). In either study, there was no significant association with TZD exposure and fracturesamong men.

A change in BMD was identified in two randomized controlled trials and two observational studies. TZD therapy was associated with a consistent decline in BMD as compared with controls. A significant reduction in BMD at the lumbar spine and at the hip was observed among women who used TZD therapy. The percent change in BMD with weighted mean difference was -1.11% (95% CI -2.08 to -0.14%; *P* = 0.02) and at the hip the weighted mean difference was -1.24% (95% CI -2.34% to -0.67%; *P* < 0.001.

The investigators interpretation of this data stated that long-term use of TZDs doubles the risk of fractures among women with type 2 diabetes, without a significant increase in risk of fractures among men with type 2 diabetes.

Observational Study Exploring Fractures with Thiazolidinedione Use

An observational, nested, case-controlled study in a UK-based general practice research database compared the risk of fractures in men and women with type 2 diabetes receiving thiazolidinediones (TZDs) to those on other oral antidiabetic drugs (OADs).(86) Between January 1994 and December 2005, individuals who received at least one prescription for a TZD, sulfonylurea, biguanide, alpha glucosidase inhibitor, or prandial glucose regulator, with or without concomitant insulin use (n = 50,048) and adults with type 2 diabetes who never received a prescription for an OAD or insulin (n = 16,648) were identified as study population. From this population, 1,020 patients with a first time diagnosis of low trauma fractures were identified and 3,728 control subjects without fracture diagnosis were randomly selected to match patients with fracture.

Clinically diagnosed low-trauma fractures consisted of wrist/forearm (301), hip (274), humerus (222), rib (148), vertebral (56) and others (19).(86) Of the 1,020 case patients with fracture, 65 subjects used thiazolidinediones (TZDs), all in combination with other oral antidiabetic drugs (OADs). After adjustments, including age, body mass index, other antidiabetic drugs, concomitant medications, and comorbidities, the odds ratio (OR) for current users of 8 or more TZD prescriptions, corresponding to 12-18 months of therapy, compared with non users was 2.43 [95% confidence interval (CI): 1.49 – 3.95]. The highest risk estimate was seen in users of 15 or more prescriptions, corresponding to 2 or more years of therapy [2.86 (95% CI: 1.57 - 5.22); *P* < 0.001]. The adjusted odds ratio on fracture risk for current users of 8 or more prescriptions of *Avandia* or pioglitazone was 2.38 (95% CI: 1.39 - 4.09) and 2.59 (95% CI: 0.96 - 7.01), respectively. In addition, the adjusted odds ratio for current users of 8 or more TZD prescriptions stratified by sex was 2.50 (95% CI 0.84-7.41) for men and 2.56 (95% CI 1.43-4.58) for women. In contrast to the observations in ADOPT (A Diabetes Outcome Progression Trial), risk of fracture also increased in men and TZD use was associated with an increased risk of hip and nonvertebral osteoporosis fractures in both men and women.

Reports of Anemia or Decreased Hemoglobin or Hematocrit with Avandia

Clinical Information

The percentage of patients experiencing anemia during pre-approval, double-blind clinical trials for *Avandia* are noted in Table 12.(51,87,67,88,52,89,48,49,50,53,54,55,90,91)

Table 12. Incidence of Anemia During Pre-Approval, Double-Blind Clinical Trials*

Regimen	Incidence (%)
Monotherapy	
Avandia† (n = 2526)	1.9
Placebo (n = 601)	0.7
Combination Metformin	
Avandia 4 or 8 mg/day + Metformin (n = 338)	7.1
Metformin (n = 225)	2.2
Combination Sulfonylurea	
Avandia 4 or 8 mg/day + Sulfonylurea (n = 1507)	2.3
Sulfonylurea (n = 1213)	0.6
Combination Insulin	
Avandia 4 mg/day + Insulin (n = 206)	7.3
Insulin (n = 203)	3.4
Combination Sulfonylurea and Metformin	
*All randomized population; † Includes all doses studied, majority of patients received *Avandia* 4 or 8 mg/day.	

Regimen	Incidence (%)
Avandia 4 or 8 mg/day + Sulfonylurea + Metformin (n = 561)	6.7
Metformin + Sulfonylurea (n = 276)	0.4
*All randomized population; † Includes all doses studied, majority of patients received *Avandia* 4 or 8 mg/day.	

In double-blind studies, anemia was reported in 1.9% of patients receiving *Avandia* as monotherapy [51,52,48,49,50,53,54,55] compared to 0.7% on placebo[48,49,53,54,55], 0.6% on sulfonylureas[88,52,89], and 2.2% on metformin[51,87]. In clinical trials, edema was reported in 4.8% of patients receiving *Avandia* as monotherapy[51,52,48,49,50,53,54,55] compared to 1.3% on placebo[48,49,53,54,55], 1.0% on sulfonylureas[88,52,89], and 2.2% on metformin[51,87]. The incidence of anemia was greater in patients treated with *Avandia* in combination with metformin, insulin, or metformin plus a sulfonylurea compared to either *Avandia* monotherapy or in combination with a sulfonylurea. Lower pre-treatment hemoglobin/hematocrit levels in patients enrolled in the metformin combination[51,87] and insulin combination clinical trials[90,91] may have contributed to the higher reporting rate of anemia in these studies.

Across all controlled clinical studies, decreases in hemoglobin and hematocrit (mean decreases in individual studies ≤ 1 gm/dL and ≤ 3.3%, respectively) were observed for *Avandia* alone and in combination with other hypoglycemic agents. [51,87,48,49,50,53,54,55] The changes occurred primarily during the first 3 months following initiation of *Avandia* therapy or following an increase in *Avandia* dose. The observed changes may be related to the increased plasma volume observed with *Avandia* treatment and may be dose-related.[92] Cases of anemia were generally mild to moderate in severity and usually did not require discontinuation of treatment.

4.12 Other Clinical Considerations

Pharmacokinetics of Avandia in Patients with Hepatic Impairment

In a single-dose, open-label trial, the pharmacokinetics of rosiglitazone 8 mg (2 x 4 mg tablets) were evaluated in 17 healthy subjects and 18 subjects with chronic hepatic impairment [Child-Pugh Score ≥ 6 (range 6 - 11)].[93,94] Patients with hepatic disease were included if they had a clinical history of cirrhosis diagnosed either by liver biopsy and/or a liver/spleen scan; a history consistent with cirrhosis (i.e., esophageal varices, portal hypertension, or ascites); or a clinical history of chronic hepatic insufficiency diagnosed by clinical laboratory tests. Subjects participating in this trial were generally young males ranging in age from 31 to 59 years. Blood samples were obtained pre-dose and at various times up to 96 hours after dosing. The pharmacokinetic parameters of rosiglitazone following a single 8 mg dose are provided in Table 1.

Table 13. Mean (SD) Pharmacokinetic Parameters Following a Single-dose of Rosiglitazone 8 mg[93,94]

Parameter (units)	Hepatic Impairment (n = 18)	Healthy Volunteers (n = 17)
$AUC_{(0\text{-inf})}$ (ng h/ml)	3576 (1083)	2645 (677)
Cmax (ng/ml)	407 (119)	506 (104)
Tmax (h)*	1.00 (0.48-4.00)	1.00 (0.50-2.00)
$T_{1/2}$ (h)	6.03 (2.10)	3.79 (1.03)
Fraction Unbound	0.27 (0.12)	0.12 (0.03)
U. $AUC_{(0\text{-inf})}$ (ng h/ml)	9.88 (5.31)	3.20 (1.37)
U. Cmax (ng/ml)	1.09 (0.52)	0.61 (0.20)
* median (range).		
AUC = area under the curve; Cmax = maximum concentration;SD = standard deviation;Tmax = time to maximum concentration;$T_{1/2}$= elimination half-life;U = Unbound.		

As a result of a decrease in oral clearance, mean exposure to rosiglitazone (total and unbound) was higher in patients with hepatic impairment, compared to healthy volunteers.[93] The observed changes in total Cmax (21% decrease) and total AUC (34% increase) in patients with hepatic dysfunction compared to healthy subjects were reflective of the observed changes in free fraction and free intrinsic clearance. The unbound fraction of rosiglitazone was increased approximately two-fold and unbound AUC and Cmax were increased approximately 188% and 70%; respectively, in patients with hepatic impairment. As expected, mean serum albumin concentrations in patients with hepatic impairment were lower than those reported for the healthy volunteers (3.0 vs. 4.3 g/dL, respectively). Rosiglitazone is normally highly bound (~99.8%) to human serum albumin. The $T_{1/2}$ in patients with hepatic impairment was prolonged on average by 2 hours; however, Tmax was similar to the values observed in the control group. The single dose of rosiglitazone was well tolerated with the most common adverse event being headache. In addition, there were no changes in vital signs, electrocardiograph interval values or laboratory values of potential clinical concern related to rosiglitazone administration.(93) The safety of multiple doses of *Avandia* in patients with liver impairment has not been evaluated.

4.13 Drug/Food/Disease Interactions

Refer to Enclosed Prescribing Information.

4.14 Dosing and Administration

Refer to Enclosed Prescribing Information.

5. EFFICACY AND SAFETY TRIALS (FDA APPROVED)

5.1 Efficacy and Safety of *Avandia* Monotherapy

Background

A total of 2,315 patients with type 2 diabetes, previously treated with diet alone or antidiabetic medication(s), were treated with *Avandia* as monotherapy in 6 double-blind studies, which included two 26-week placebo-controlled studies(48,49), one 52-week glyburide-controlled study(50), and 3 placebo-controlled dose-ranging studies (53,54,55) of 8 to 12 weeks duration. Previous antidiabetic medication(s) were withdrawn and patients entered a 2 to 4 week placebo run-in period prior to randomization.

Efficacy

Short-term Trials

Two 26-week, double-blind, placebo-controlled trials, in patients with type 2 diabetes (n = 1,401) with inadequate glycemic control (mean baseline fasting plasma glucose approximately 228 mg/dL [101 to 425 mg/dL] and mean baseline HbA1c 8.9% [5.2% to 16.2%]), were conducted.(48,49) Treatment with *Avandia* produced statistically significant improvements in fasting plasma glucose (FPG) and HbA1c compared to baseline and relative to placebo. Data from one of these studies are summarized in Table 14.

Table 14. Glycemic Parameters in a 26-Week Placebo-Controlled Trial(48,49)

	Placebo	*Avandia*		*Avandia*	
		4 mg once daily	2 mg twice daily	8 mg once daily	4 mg once daily
N	173	180	186	181	187
FPG (mg/dL)					
Baseline (mean)	225	229	225	228	228
Change from baseline (mean)	8	-25	-35	-42	-55
Difference from placebo (adjusted mean)	-	-31*	-43*	-49*	-62*
% of patients with ≥30 mg/dL decrease from baseline	19%	45%	54%	58%	70%
HbA1c (%)					
Baseline (mean)	8.9	8.9	8.9	8.9	9.0
Change from baseline (mean)	0.8	0.0	-0.1	-0.3	-0.7
Difference from placebo (adjusted mean)	-	-0.8*	-0.9*	-1.1*	-1.5*

	Placebo	*Avandia*		*Avandia*	
		4 mg once daily	2 mg twice daily	8 mg once daily	4 mg once daily
% of patients with ≥0.7% decrease from baseline	9%	28%	29%	39%	54%
FPG - fasting plasma glucose; * $P < 0.0001$ compared to placebo					

When administered at the same total daily dose, *Avandia* was generally more effective in reducing FPG and HbA1c when administered in divided doses twice daily compared to once daily doses.[48,49] However, for HbA1c, the difference between the 4 mg once daily and 2 mg twice daily doses was not statistically significant.

Safety

The incidence and types of adverse events reported in the pivotal clinical trials of *Avandia* as monotherapy are shown in Table 15.

Table 15. Adverse Events (≥5% in Any Treatment Group) Reported by Patients in Double-Blind Clinical Trials with *Avandia* as Monotherapy[51,87,88,52,89,48,49,50,53,54,55]

Preferred Term	*Avandia* Monotherapy N=2,526	Placebo N = 601	Metformin N = 225	Sulfonylureas* N = 626
	%	%	%	%
Upper respiratory tract infection	9.9	8.7	8.9	7.3
Injury	7.6	4.3	7.6	6.1
Headache	5.9	5.0	8.9	5.4
Back Pain	4.0	3.8	4.0	5.0
Hyperglycemia	3.9	5.7	4.4	8.1
Fatigue	3.6	5.0	4.0	1.9
Sinusitis	3.2	4.5	5.3	3.0
Diarrhea	2.3	3.3	15.6	3.0
Hypoglycemia	0.6	0.2	1.3	5.9
* Includes patients receiving glyburide (N = 514), gliclazide (N = 91), or glipizide (N = 21).				

In double-blind studies, anemia was reported in 1.9% of patients receiving *Avandia* as monotherapy [51,52,48,49,50,53,54,55] compared to 0.7% on placebo[48,49,53,54,55], 0.6% on sulfonylureas[88,52,89], and 2.2% on metformin[51,87]. In clinical trials, edema was reported in 4.8% of patients receiving *Avandia* as monotherapy[51,52,48,49,50,53,54,55] compared to 1.3% on placebo[48,49,53,54,55], 1.0% on sulfonylureas[88,52,89], and 2.2% on metformin[51,87]. Anemia and edema tended to be reported more frequently at higher doses, and were generally mild to moderate in severity and usually did not require discontinuation of treatment with *Avandia*.

Long-term Trials

For long-term efficacy and safety data with *Avandia* monotherapy in patients recently diagnosed with type 2 diabetes, please refer to the data from A Diabetes Outcome Progression Trial (ADOPT) contained in *Results of the ADOPT Trial*

5.2 Efficacy and Safety of *Avandia* Add-on Therapy with Metformin in Type 2 Diabetes

The use of *Avandia* in combination with metformin was evaluated in two pivotal, 26-week, randomized, double-blind studies involving over 670 patients with type 2 diabetes. [51,87] Patients in both studies were randomized to one of three treatment regimens (described in Table 16) after completing the following steps:

- **Metformin Titration Period** - Patients naïve to metformin and those entering the study on sub-maximal doses of metformin entered a dose escalation period. Doses were increased by 500 mg/week to a maximum dose of 2500 mg/day.
- **Metformin Maintenance/Placebo Run-In Period** – Patients then entered a 4-week trial of diet/exercise reinforcement in addition to the maximum recommended metformin dose (2500

mg/day) in order to identify those patients who were inadequately controlled (fasting plasma glucose [FPG] ≥ 140mg/dL and ≤300mg/dL). Only those patients inadequately controlled on metformin therapy were eligible for randomization.

Avandia 4 or 8 mg/day in combination with metformin significantly reduced HbA1c and FPG compared to baseline and metformin alone. The most common adverse events (>5%) reported in patients treated with *Avandia* in combination with metformin were upper respiratory tract infection, injury, headache, fatigue, sinusitis, diarrhea and anemia. Overall, these events were generally mild to moderate in severity and usually did not require discontinuation of treatment. A summary of the efficacy and safety results are presented in Table 16 and Table 17.

Table 16. Evaluation of *Avandia* in Combination with Metformin - Pivotal Clinical Studies (51,87)

Study Design/ Baseline Characteristics	n (ITT)	Regimen	Baseline HbA1c (%) / FPG (mg/dL)	Primary Endpoint HbA1c (%)		Secondary Endpoints FPG (mg/dL)	
				Mean Difference from Baseline	Mean Difference from Comparator	Mean Difference from Baseline	Mean Difference from Comparator
Study 094 26-week, R, DB, PC Age 58 yrs, 68% male, BMI 30 kg/m², 80% white, duration of disease: 8 yrs, U.S.	113	MET + PBO	8.6/214	0.5*	NA	6	NA
	116	RSG 4 mg QD + MET	8.9/215	-0.6*	-1.0*	-33*	-40*
	110	RSG 8 mg QD + MET	8.9/220	-0.8*	-1.2*	-48*	-53*
Study 093 26-week, R, DB, Age 59 yrs, 61% male, BMI 31 kg/m², 79% white, duration of disease: 7 yrs, U.S.	106	MET + PBO	8.8/210	0.1	-0.8†	6	-56†
	95	RSG 4 mg BID + PBO	8.7/206	1.3*	-2.0†	30*	-80†
	105‡	RSG 4 mg BID + MET §	8.7/217	-0.7*	NA	-52*	NA

BMI = body mass index; DB = double-blind; FPG = fasting plasma glucose; ITT = intent=to-treat; MET = metformin; NA = not applicable; PBO = placebo; PC = placebo-controlled; R= randomized; RSG = rosiglitazone; URTI= upper respiratory tract infection; U.S. = United States.

* $P < 0.0001$; † $P < 0.0001$ vs. *Avandia* + MET; ‡ n = 103 for HbA1c; § A rise in HbA1c in the *Avandia* plus placebo and metformin plus placebo groups was observed in this study. These results may reflect the particular design of the study. Approximately 50% of patients had been previously treated with more than one oral antidiabetic agent. Combination therapy was withdrawn at study entry, and patients were titrated to maximal dose metformin. Only patients inadequately controlled on maximal dose metformin were then randomized. Because of the limitations in study design, comparisons between the two monotherapy arms in this study are not appropriate.

Table 17. Adverse Events Reported During the Pivotal Clinical Studies of *Avandia* in Combination with Metformin[51,87]*

	RSG 4 mg/day + MET	RSG 8 mg/day‡ + MET	RSG 8 mg/day§	MET
	N = 119	N = 219	N = 107	N = 225
Preferred Term	%	%	%	%
URTI	16	16	17.8	8.9
Diarrhea	12.6	12.8	4.7	15.6
Anemia	5.9	7.8	0.9	2.2
Injury†	10.1	6.8	12.1	7.6
Sinusitis	5	6.8	4.7	5.3
Headache	6.7	6.4	4.7	8.9
Back Pain	3.4	5.9	2.8	4
Fatigue	6.7	5.5	4.7	4
Arthralgia	5	5	1.9	2.2
Pain	3.4	4.6	6.5	4
Infection Viral	5.9	4.6	3.7	3.6
Nausea	5	3.7	2.8	3.1
Urinary Tract Infection	3.4	2.7	5.6	3.1
Hypercholesterolemia	1.7	2.3	7.5	1.3
Hyperglycemia	2.5	1.8	16.8	4.4
Hypertension Aggravated	2.5	0.9	0.9	5.3
Micturition Frequency	0.8	0.9	5.6	2.2

MET = metformin; RSG = rosiglitazone; URTI = upper respiratory tract infection.

* Pooled results of on-therapy adverse events occurring in > 5% of patients in any treatment group; † Injury includes items such as cuts, burns, sprains, fractures, accidents, and surgical procedures; ‡ Patients may have received the total dose once daily or in divided doses twice daily; § treatment arm included in Study 093.

Gomez-Perez et al conducted a 26-week, randomized, double-blind, placebo-controlled study in 116 Mexican patients to evaluate the efficacy and safety of *Avandia* in combination with metformin. [95] Patients inadequately controlled with metformin 2500 mg/day, continued on open-label metformin and were randomized in a double-blind manner to add-on therapy with *Avandia* 2 mg twice daily, *Avandia* 4 mg twice daily, or placebo. All analyses were conducted with the intent-to-treat group that included 105 patients. Baseline characteristics were similar in the three groups. A summary of glycemic efficacy results are presented in Table 18.

Table 18. Glycemic Results in Mexican Patients at 26 weeks [95]

	RSG 2 mg BID + MET N = 35	RSG 4 mg BID + MET N = 36	PBO + MET N = 34
Mean change from baseline HbA1c (%)	-0.7*	-1.2*	0.3
Difference from metformin + placebo (%)	-1.0*	-1.5†	-
% Responders‡	54%	61%	24%

BID= twice daily; MET = metformin; PBO = placebo; RSG = rosiglitazone

* $P < 0.05$; †$P < 0.001$; ‡ Patients who achieved an HbA1c response defined as ≥ 0.7% reduction from baseline.

The mean FPG decreased significantly from baseline with *Avandia* 2 mg twice daily plus metformin (-45 mg/dL, $P < 0.0009$) and *Avandia* 4 mg twice daily plus metformin (-63 mg/dL, $P < 0.0001$) but increased with metformin plus placebo (+4 mg/dL, $P = 0.7143$). [95] Target FPG values (< 140 mg/dL) were achieved in 26%, 42%, and 6% of patients who received *Avandia* 2 mg twice daily plus metformin, *Avandia* 4 mg twice daily plus metformin and placebo plus metformin, respectively.

The number of adverse events was similar between groups. [95] Gastrointestinal events (diarrhea, nausea, vomiting, flatulence, or abdominal pain) were reported in 17% and 15% of *Avandia* and placebo-treated patients, respectively. Overall, edema was reported in 5% of patients who received *Avandia* and metformin, but none of the events were considered serious or resulted in study withdrawal. Four cardiac-related adverse events were reported in the study which included 1 report of bundle branch block, 1 report of myocardial ischemia, and 2 reports of bundle branch block and tachycardia in the placebo-treated, *Avandia* 2 mg plus metformin and *Avandia* 4 mg plus metformin groups, respectively. None of these cardiac-related adverse events were considered serious or resulted in study withdrawal. Mean weight increased from baseline with *Avandia* (2 mg twice daily: +0.26 kg; 4 mg twice daily: +2.42 kg) and decreased in the placebo group (-0.86 kg).

The use of *Avandia* in combination with metformin was evaluated in a 24-week, randomized, double-blind study involving over 700 patients with type 2 diabetes.[96] The primary objective of the study was to evaluate the non-inferiority of adding *Avandia* 4 mg twice daily to submaximal doses of metformin (1000 mg/day) relative to up-titrated metformin monotherapy (2000 mg/day) in achieving glycemic control.

Patients enrolled into the study included drug naïve patients as well as patients treated with monotherapy or combination antidiabetic agents.[96] After a 2-week washout period, patients received open-label metformin, which was uptitrated to a dose of 1000 mg/day over 4-7 weeks. After the metformin titration period, patients entered a 24-week, double-blind phase and were randomized to receive either *Avandia* 2 mg twice daily plus open-label metformin 1000 mg/day (n = 382) or metformin monotherapy (blinded-metformin 500 mg plus open-label metformin 1000 mg) (n = 384). At week 8, patients had their blinded medication increased: *Avandia* 2 mg twice daily increased to 4 mg twice daily and metformin 500 mg/day increased to 1000 mg/day.

Baseline demographics were similar between groups. [96,97] The majority of patients were male (51%) and white (72%), with a mean age of 56 years and a mean BMI of 34 kg/m^2.

The primary endpoint was to compare the mean change in HbA1c from baseline to week 24 between groups. [96] Secondary endpoints included change in FPG and the percent of patients reaching American Diabetes Association (ADA) and American Association of Clinical Endocrinologists (AACE) HbA1c goals. Changes in HbA1c and FPG from baseline to Week 24 for the intent-to-treat completer population are provided in Table 19.

Table 19. Change in HbA1c and FPG [96,97] *

Parameter	MET 2000 mg/day	*Avandia* 4 mg BID + MET 1000 mg/day
HbA1c (%)		
n	277	296
Baseline (mean)	7.9	8
Change from baseline (mean)	-0.7	-0.9
Difference from MET (95% CI)	-	-0.2 (-0.36, - 0.04)†
FPG (mmol/L)		
n	237	238
Baseline (mean)	171	181
Change from baseline (mean)	-20	-41
Difference from MET (95% CI)		-15 (-22.1, -8.5)‡

BID = twice daily; FPG = fasting plasma glucose; MET = metformin; RSG = rosiglitazone.

*Intent-to-treat completers; † RSG 4 mg BID + MET 1000 mg/day was found to be as effective as MET 2000 mg/day in improving HbA1c: ‡*P* value vs. MET < 0.0001

At week 24, the difference in mean HbA1c between groups demonstrated that *Avandia* plus submaximal metformin (1000 mg/day) was as effective as uptitrated metformin (2000 mg/day) monotherapy. [96] A greater percentage of patients who received *Avandia* plus submaximal metformin were able to achieve the ADA HbA1c goal of < 7% compared to patients who received uptitrated metformin monotherapy (58%

vs. 48%, respectively). Additionally, 41% of patients in the combination group were able to achieve the AACE HbA1c goal of ≤ 6.5% compared to 28% in the uptitrated metformin alone group.

The most commonly reported adverse events (≥ 5%) in patients who received *Avandia* plus sub-maximal metformin included URTI, diarrhea, abdominal pain, dyspepsia, flatulence, and injury.[97] Patients treated with *Avandia* plus submaximal metformin reported fewer GI adverse events than those treated with uptitrated metformin monotherapy (28.5% vs. 39.1% , respectively). The odds of experiencing a GI adverse event were 63% greater with uptitrated metformin monotherapy compared to *Avandia* plus submaximal metformin ($P = 0.0023$). [96] Fewer patients in the combination group compared to those treated with uptitrated metformin monotherapy discontinued therapy due to GI effects (3.1% vs. 6.8%).

The incidence of edema was 4.7% with *Avandia* plus submaximal metformin vs. 1.3% with uptitrated metformin monotherapy.[97] [96] The percentage of patients who discontinued due to edema was 0.5% and 0% with *Avandia* plus submaximal metformin and uptitrated metformin monotherapy, respectively. Patients treated with *Avandia* plus submaximal metformin reported more cardiac ischemic adverse events than those treated with uptitrated metformin monotherapy (1.3% vs. 0.8% , respectively). Two patients from the *Avandia* plus submaximal metformin group withdrew due to a myocardial infarction and one in the uptitrated metformin group withdrew due to coronary artery disease.

From baseline to week 24, an increase in mean body weight (+1.79 kg) was observed with *Avandia* plus submaximal metformin (n = 297), whereas a decrease in mean body weight (-1.78 kg) was observed with uptitrated metformin monotherapy (n = 292). In the combination group, 55% of patients experienced a 0 to < 2 kg increase in weight.[97] [96]

5.3 Efficacy and Safety of *Avandia* Add-on Therapy to a Sulfonylurea for the Treatment of Type 2 Diabetes Mellitus

Avandia Add-on Therapy to a Sulfonylurea

The safety and efficacy of *Avandia* added to a sulfonylurea has been studied in clinical trials in patients with type 2 diabetes inadequately controlled on sulfonylureas alone. No clinical trials have been conducted with the fixed-dose combination tablet *Avandaryl* as a second-line therapy (i.e., in patients inadequately controlled on sulfonylurea or who have initially responded to *Avandia* alone and require additional glycemic control).

A total of 3,457 patients with type 2 diabetes participated in ten 24 to 26 week randomized, double blind, placebo/active controlled studies and one 2-year double-blind, active-controlled study in elderly patients designed to assess the efficacy and safety of *Avandia* in combination with a sulfonylurea.[98,88,52,89,99,100,101,102,103,104,105] *Avandia* 2 mg, 4 mg, or 8 mg daily, was administered either once daily (3 studies) or in divided doses twice daily (7 studies), to patients inadequately controlled on a submaximal or maximal dose of sulfonylurea. In these studies, the combination of *Avandia* 4 mg or 8 mg daily (administered as single or twice daily divided doses) and a sulfonylurea significantly reduced fasting plasma glucose (FPG) and HbA1c compared to placebo plus sulfonylurea or further up titration of the sulfonylurea. Table 20 and Table 21 show pooled data for 8 studies in which *Avandia* added to sulfonylurea was compared to placebo plus sulfonylurea.

Table 20. Effects of Twice Daily *Avandia* Plus a Sulfonylurea on FPG and HbA1c in 24- to 26- Week Combination Studies(52,89,100,103,104)

Twice Daily Divided Dosing (5 studies)	Sulfonylurea	*Avandia* 2 mg twice daily + sulfonylurea	Sulfonylurea	*Avandia* 4 mg twice daily + sulfonylurea
N	397	497	248	346
FPG (mg/dL)				
Baseline (mean)	204	198	188	187
Change from baseline (mean)	11	-29	8	-43
Difference from sulfonylurea alone (adjusted mean)	-	-42*	-	-53*
% of patients with ≥30 mg/dL decrease from baseline	17%	49%	15%	61%
HbA1c				
Baseline (mean)	9.4	9.5	9.3	9.6
Change from baseline (mean)	0.2	-1.0	0.0	-1.6
Difference from sulfonylurea alone (adjusted mean)	-	-1.1*	-	-1.4*
% of patients with ≥0.7% decrease from baseline	21%	60%	23%	75%
* $P \leq 0.0001$ compared to sulfonylurea alone.				

Table 21. Effects of Once Daily *Avandia* Plus a Sulfonylurea on FPG and HbA1c in 24- to 26- Week Combination Studies(88,102,105)

Once Daily Dosing (3 studies)	Sulfonylurea	*Avandia* 4 mg once daily + sulfonylurea	Sulfonylurea	*Avandia* 8 mg once daily + sulfonylurea
N	172	172	173	176
FPG (mg/dL)				
Baseline (mean)	198	206	188	192
Change from baseline (mean)	17	-25	17	-43
Difference from sulfonylurea alone (adjusted mean)	-	-47*	-	-66*
% of patients with ≥30 mg/dL decrease from baseline	17%	48%	19%	55%
HbA1c (%)				
Baseline (mean)	8.6	8.8	8.9	8.9
Change from baseline (mean)	0.4	-0.5	0.1	-1.2
Difference from sulfonylurea alone (adjusted mean)	-	-0.9*	-	-1.4*
% of patients with ≥0.7% decrease from baseline	11%	36%	20%	68%
* $P \leq 0.0001$ compared to sulfonylurea alone.				

One of the 24 to 26 week studies included patients who were inadequately controlled on maximal doses of glyburide and switched to *Avandia* 4 mg daily as monotherapy; in this group, loss of glycemic control was demonstrated, as evidenced by increases in FPG and HbA1c.[52]

Pooled results (Studies 127, 132, 143, 145, 147, 162, 015, 079, 096) of on-therapy adverse events occurring in >3% of patients in any treatment group during the 24- to 26-week studies in which *Avandia* was added to sulfonylurea therapy are presented in Table 22.

Table 22. Pooled Adverse Events from Nine 24- to 26-week *Avandia* Plus Sulfonylurea Combination Studies[88,52,89,99,100,101,102,103,104]

	***Avandia* 4 mg/day + Sulfonylurea** N = 622	***Avandia* 8 mg/day + Sulfonylurea** N = 885	**Sulfonylurea** N = 1213
Preferred Term	%	%	%
Edema*	7.4	12.4	1.6
Hypoglycemia	6.6	11.8	3.1
Weight Increase	4.3	9.6	1.0
Pain†	3.5	6.8	5.7
URTI	11.6	7.1	7.0
Urinary Tract Infection	6.1	4.4	3.3
Hyperlipemia	4.8	4.2	0.7
Injury‡	4.7	3.8	5.0
Dizziness	4.8	3.4	2.8
Anemia	1.3	3.1	0.7
Arthralgia	3.4	2.9	1.9
Headache	4.0	2.7	4.5
Hypercholesterolemia	3.7	2.6	0.9
Hyperglycemia	2.7	0.5	6.1

*Edema includes edema dependent, edema legs, edema peripheral, and edema generalized; † Pain includes pain and back pain; ‡ Injury includes items such as cuts, burns, sprains, fractures, accidents, and surgical procedures.

URTI = Upper respiratory tract infection.

As part of its ongoing monitoring and assessment of the safety of *Avandia*, GlaxoSmithKline proactively conducted a series of retrospective analyses to characterize the degree of association, if any, between *Avandia* and events of congestive heart failure (CHF) and myocardial ischemia.[11] Forty-two controlled and blinded clinical trials in which 4 mg or 8 mg doses of *Avandia* was used were included in the analysis. Observations regarding CHF and *Avandia* therapy remain consistent with reports and observations from individual and integrated controlled clinical trials of an increased incidence of CHF in patients treated with *Avandia* and sulfonylurea combinations.

Study 325

A 24-week, randomized, double-blind, placebo-controlled study (Study 325) evaluated the efficacy and safety of *Avandia* in combination with submaximal therapeutic doses of glimepiride in 391 patients with type 2 diabetes inadequately controlled on non-thiazolidinedione oral antidiabetic monotherapy.[106] During a 6-week run-in period patients discontinued their current antidiabetic medication and received glimepiride 2 mg/day plus placebo. All patients were randomized to receive *Avandia* 4 mg/day plus glimepiride 2 mg/day (titratable to 4 mg/day after 8 weeks) or glimepiride 4 mg/day (titratable to 8 mg/day after 8 weeks) plus placebo for 24 weeks. The primary efficacy parameter of the study was change in HbA1c from baseline to week 24. Results are presented in Table 23.

Table 23. Evaluation of *Avandia* in Combination with Glimepiride vs Uptitrated Glimepiride[106]

Study Design/ Mean Baseline Characteristics	Regimen	Baseline HbA1c (%)/FPG (mg/dL)	Primary Endpoint HbA1c (%)		Secondary Endpoint FPG (mg/dL)	
R, DB, PC 24 weeks Age 53.5 yrs 56.6% male	Intent-to-treat population		Mean Difference from Baseline	Mean Difference from glimepiride + placebo	Mean Difference from Baseline	Mean Difference from glimepiride + placebo
	n = 181 *Avandia* 4 mg QD + glimepiride	8.15/190.9	-0.68*	-0.56†	-27.7*	-24.5†
	n = 181 glimepiride + placebo	8.01/183.6	-0.08	-	-0.6	-
* Significant change vs. baseline (*P* < 0.0001); † Significant vs. glimepiride + placebo (*P* < 0.0001). DB = Double-blind; FPG = Fasting plasma glucose; HbA1c = glycosylated hemoglobin; PC = Placebo-controlled; QD = Once daily; R = Randomized.						

Overall, the most common adverse events (> 4%) reported among all randomized patients were hypoglycemia (*Avandia* + glimepiride 20.9%; glimepiride + placebo 13.3%), nasopharyngitis (*Avandia* + glimepiride 5.1%; glimepiride + placebo 9.7% and peripheral edema (*Avandia* + glimepiride 4.1%; glimepiride + placebo 5.6%).[106] One patient in the glimepiride + placebo uptitration group withdrew due to severe hypoglycemia. Weight gain was reported by 3.6% of patients treated with *Avandia* plus glimepiride and 0.5% of patients treated with glimepiride plus placebo.

5.4 Efficacy and Safety of *Avandia* in Combination with Metformin and SU

Clinical data

Triple Therapy with *Avandia*, a Sulfonylurea, and Metformin

Jones et al [7,67,107] reported on the effectiveness and tolerability of *Avandia* in combination with a sulfonylurea and metformin in type 2 diabetes patients. Patients on at least half-maximal doses of glyburide and metformin were titrated to glyburide 20 mg/day and metformin 2 g/day prior to entering a 4-week, single-blind, placebo run-in period.[67] A total of 837 patients were randomized to receive placebo, *Avandia* 2 mg twice daily, or *Avandia* 4 mg twice daily in addition to glyburide and metformin. After 26 weeks of treatment, significant reductions in mean HbA1c and FPG from placebo were observed in both groups receiving *Avandia* in addition to glyburide and metformin. Results are presented in Table 24.

Table 24. Effect of *Avandia* in Combination with Glyburide and Metformin [7,67,107]

	***Avandia* 2 mg BID + Glyburide + Metformin** **n = 276**	***Avandia* 4 mg BID + Glyburide + Metformin** **n = 277**	**Placebo + Glyburide + Metformin** **n= 273**	

HbA1c (%)			
Mean baseline	8.6	8.7	8.7
Mean change from baseline	-0.4*	-0.9*	0.2†
Mean change from placebo	-0.6*	-1.1*	-
% with ≥ 0.7% decrease from baseline	39‡	63‡	16
FPG (mg/dL)			
Mean baseline	190	192	189
Mean change from baseline	-19*	-40*	14*
Mean change from placebo	-30*	-52*	-
% with ≥ 30 mg/dL decrease from baseline	46‡	62‡	16
*$P < 0.0001$; † $P = 0.005$; ‡ $P = 0.0001$ vs. placebo.			

The percentage (≈ 80%) of adverse events reported was similar in each group.(67) Symptoms of hypoglycemia were more commonly reported in the groups receiving *Avandia* [4 mg/day: 27% (75/281); 8 mg/day: 35% (97/280); placebo: 10% (27/276)]. Recurrent episodes of hypoglycemia appeared to be effectively managed by reducing the dose of glyburide and/or metformin. Mild to moderate edema was also reported more frequently in the *Avandia* (4 mg/day: 10%; 8 mg/day: 14.3%; placebo: 4.0%) but infrequently resulted in withdrawal from therapy. Anemia was reported in 3.6%, 10%, and 0.4% of patients receiving *Avandia* 4 mg/day, *Avandia* 8 mg/day, and placebo, respectively. Cardiac failure was reported in 1.8 %, 1.1 %, and 0.4 % of patients receiving *Avandia* 4 mg/day, 8 mg/day, and placebo, respectively. (67) Of these events, three (n = 2; *Avandia* 4mg/day; n = 1; *Avandia* 8mg/day) were categorized as serious adverse events. Additionally, cardiac ischemic events were reported in 0.4 %, 1.1 %, and 1.1 % of patients receiving *Avandia* 4 mg/day, 8 mg/day, and placebo, respectively. One patient receiving placebo was withdrawn from the study due to cardiac ischemic events. Mean weight was increased by 3.1 kg and 5.1 kg with *Avandia* 4 mg/day and 8 mg/day, respectively and was unchanged in the placebo group.

A 24-week, randomized, double-blind, placebo-controlled trial reported on the effectiveness of adding *Avandia* to the therapy of patients inadequately controlled with glyburide/metformin tablets.(7,108,109) Patients not controlled on existing antihyperglycemic monotherapy or combination therapy were enrolled in a 2- to 12-week open-label period in which they were administered glyburide/metformin tablets titrated up to 10 mg/2000 mg.(109) Patients failing to achieve glycemic control on a daily glyburide/metformin dose of at least 7.5 mg/1500 mg were randomized to receive glyburide/metformin tablets plus *Avandia* (n = 181) or placebo (n = 184) for 24 weeks. Patients initially received *Avandia* 4 mg once daily followed by dose titration up to 8 mg daily based on the glycemic response. The mean final doses of glyburide/metformin tablets were similar between groups.(108,109) A significant reduction versus placebo was observed in HbA1c with glyburide/metformin plus *Avandia*. In addition, the combination of glyburide/metformin plus *Avandia* significantly reduced FPG compared to placebo. Study results are presented in Table 25.

Table 25. Efficacy of Glyburide/Metformin Tablets in Combination with *Avandia* or Placebo after 24 Weeks(108,109)

	HbA1c (%)		**FPG (mg/dL)**	
	Placebo + Gly/Met n = 178	***Avandia* +Gly/Met n = 177**	**Placebo + Gly/Met n = 181**	***Avandia* + Gly/Met n = 176**
Mean baseline	8.1	8.1	173.1	178.4
Mean change vs. baseline	0.1	-0.9*	7	-41*
Mean change vs. comparator	-	-1*	-	-48.5*
Patients with final HbA1c < 7%	13.50%	42.4%	-	-
Gly/Met = glyburide/metformin tablets. * $P < 0.001$.				

In general, the incidence of adverse events was similar for the two treatment groups.[110] Edema was observed in 14 of 181 (7.7%) patients receiving glyburide/metformin plus *Avandia* and 4 of 184 (2.2%) patients receiving glyburide/metformin plus placebo with no reports considered serious. [108,110] Blood glucose values ≤ 50 mg/dL were recorded in 22% and 3.3% of patients receiving glyburide/metformin plus *Avandia* or glyburide/metformin plus placebo, respectively. However, neither group experienced hypoglycemia requiring pharmacologic therapy or assistance of a third party. Mean body weight increased by 3 kg and 0.03 kg from baseline with *Avandia* and placebo, respectively.

An open-label extension phase of this study evaluated the effects of *Avandia* with glyburide/metformin for an additional 20 weeks (n = 313).[111] Patients who were previously randomized to receive glyburide/metformin plus *Avandia* maintained glycemic control over 44 weeks, achieving a mean HbA1c < 7%. Similar efficacy was noted in patients who were previously randomized to glyburide/metformin plus placebo when *Avandia* was added. Of all patients who completed 20 weeks of triple therapy, 62.5% (172/275) achieved an HbA1c < 7% at study end. Adverse events were reported by 63% of patients. Symptoms of hypoglycemia were reported in 44% of patients and were generally considered moderate in nature.

Kiayias et al evaluated the effectiveness of adding *Avandia* to glimepiride and metformin. Thirty-eight patients inadequately controlled on maximum doses of glimepiride (6 mg/day) and metformin (2550 mg/day) were divided into two groups (baseline HbA1c ≈ 9%). [112] The first group (n = 19) received *Avandia* 4 mg/day and the second group (n = 19) received *Avandia* 8 mg/day, in addition to existing glimepiride and metformin therapy, for 20 weeks. At week 20, a significant ($P < 0.0001$) decrease in HbA1c was noted in both groups (final HbA1c of 7.8% and 7.6%, with *Avandia* 4 mg/day and *Avandia* 8 mg/day, respectively). FPG also decreased significantly in both groups. Treatment with *Avandia* was well tolerated. The most commonly reported adverse event was hypoglycemia (18.6% with *Avandia* 4 mg/day and 28% with *Avandia* 8 mg/day). Mean body weight increased by approximately 4 kg in both groups.

The long-term effectiveness of adding a TZD (initially troglitazone, later *Avandia*) in patients with an inadequate response to metformin and a sulfonylurea (n = 35) has been evaluated.[113] In an interim analysis, following a mean follow-up period of 37 months, glycemic control was maintained in the majority of patients (74%, 26/35) receiving triple therapy with a TZD, metformin, and a sulfonylurea (no insulin required). No edema, abnormalities of liver function tests, or anemia was noted. Weight gain was similar in all patients.

Bell et al further reported on the status of the patients 5 years after the initiation of the triple drug therapy regimen.[114] There were no significant differences in baseline HbA1c, BMI, or C-peptide levels between patients that failed triple drug therapy versus those that remained controlled on triple drug therapy. After 60 months, 22 of the 35 patients (63%) remained well controlled on triple drug therapy with a mean HbA1c of 7.1 ± 0.4%. The 13 patients that failed triple drug therapy and required the addition of insulin had a mean HbA1c of 8.8 ± 0.4% at 60 months. There was a significant increase from baseline in stimulated C-peptide levels in the group that remained controlled on triple drug therapy ($P = 0.05$) compared to a nonsignificant decrease in the group that failed triple drug therapy (between group comparison, $P = 0.001$). No safety information was provided from this analysis. Please note, data should be interpreted with caution as abstracts frequently present limited data and are sometimes based on early analysis. Information regarding study design and all pertinent data may not have been included in the abstract.

In a 26-week, double-blind, placebo-controlled, forced-titration study, the efficacy and safety of the addition of glimepiride in patients with type 2 diabetes inadequately controlled on combination therapy with metformin or extended release metformin plus *Avandia* or pioglitazone (n = 168) were evaluated.[115] The mean HbA1c decreased significantly ($P < 0.001$) in the glimepiride group (-1.3%) compared to the placebo group (-0.3%). A significantly greater percentage of patients in the glimepiride group reached HbA1c ≤ 7% compared with the placebo group (62.2% vs. 26%, respectively; $P < 0.001$). The most commonly reported adverse events included hypoglycemia, gastrointestinal disorders, and respiratory tract infections. Significantly more events of hypoglycemia were reported in the glimepiride group as compared with placebo (51.2 % vs. 8.3 %; $P < 0.001$). One serious report of hypoglycemia was noted in the glimepiride group but reversed with administration of oral carbohydrates. Myocardial infarction was reported in two patients receiving placebo and one receiving glimepiride, however, none of these events were considered to be related to study medication nor resulted in death. The adjusted mean difference in body mass index (BMI) between treatment groups at study end was significantly higher in the glimepiride group as compared with placebo ($P < 0.001$).

A 24-week multicenter, randomized, open-label, parallel trial, evaluated the efficacy and safety of *Avandia* (n = 112) or insulin glargine (n = 105) as add-on therapy in patients with type 2 diabetes inadequately controlled with metformin plus a sulfonylurea (SU).[116] Patients included in the study were naive to insulin therapy, greater than 18 years of age with type 2 diabetes (A1C ≥ 7.5 and ≤ 11%) and had a body mass index (BMI) of > 25 kg/m^2. Patients were also required to have been receiving treatment with stable doses of a SU (≥ 50% of the maximum recommended dose) and at least 1,000 mg metformin for ≥ 3 months prior to screening. Patients were excluded from participation in the trial for reasons that included a history of congestive heart failure, impaired renal function or having had angina pectoris or a myocardial infarction within 12 months of study entry.

The two treatment groups were well matched with respect to baseline characteristics. The mean age of this study population was approximately 55 years. Patients treated with *Avandia* had a mean baseline HbA1c of 8.7% and those treated with insulin glargine had a mean baseline HbA1c of 8.8%. This study population had a mean duration of type 2 diabetes of about 8 years.

Prior to starting the 24-week treatment phase of the trial, those patients not on maximum dose metformin were uptitrated to 2000 mg/day. Metformin and SU doses were not changed during the treatment phase of the trial. The starting dose of randomized treatment was 4 mg once daily for 6 weeks for *Avandia* and 10 units subcutaneous injection at bedtime for 7 days for insulin glargine. If the FPG was > 5.5 mmol/l after 6 weeks, *Avandia* was uptitrated to 8 mg/day. The insulin glargine dose was titrated weekly according to a prespecified protocol to achieve a target FPG of ≤ 5.5 – 6.7 mmol/l.

The primary efficacy endpoint of the study was to compare glycemic control of the *Avandia* and insulin glargine triple therapy treatment groups after 24 weeks as measured by HbA1c. Secondary endpoints included assessments of hypoglycemia, changes in FPG, body weight, and serum lipids and the proportion of patients achieving an HbA1c ≤7%. After 24 weeks, HbA1c was reduced from baseline by 1.66% and 1.51% in the insulin glargine and *Avandia* groups, respectively ($P = 0.1446$). FPG decreased from baseline to week 24 in both groups (*Avandia* -2.57 ± 0.22 mmol/l vs. insulin glargine -3.60 ± 0.23 mmol/l; $P = 0.001$). An HbA1c value of ≤ 7% was reached by 49% and 48% of patients treated with *Avandia* and insulin glargine, respectivley.

Measurements of total cholesterol, LDL, and triglycerides decreased with insulin glargine (196 to 186 mg/dl, 117 to 115 mg/dl, and 217 to 176 mg/dl). Total cholesterol, LDL and triglyceride levels increased with *Avandia* (196 to 215 mg/dl, 106 to 120 mg/dl, and 241 to 252 mg/dl). Between group differences were statistically significant ($P < 0.0012$ for each comparison). HDL increased by 4.4% ($P = 0.0407$) with *Avandia* and was unchanged with insulin glargine. Free fatty acid levels were reduced by a similar extent (insulin glargine -20.0%, *Avandia* -17.2%).

Adverse events considered possibly related to study medication were more frequently reported by patients on *Avandia* than on insulin glargine (28.6% vs. 6.7%; $P < 0.0001$). Twenty- one subjects (18.8%) in the *Avandia* triple therapy group withdrew from the study after beginning treatment versus eight (7.6%) receiving insulin glargine ($P = 0.0104$). Adverse events accounted for withdrawal of two subjects in the insulin glargine group and nine in the *Avandia* group. Serious adverse events occurred in 4.8% (5 of 105) of patients receiving insulin glargine and 9.8% (11 of 112) of patients receiving *Avandia*. Peripheral edema was reported by 12.5% vs 0% ($P = 0.001$) in the *Avandia* and insulin glargine groups, respectively. After 24 weeks, weight gain of 3.0 ± 0.4 kg and 1.7 ± 0.4 kg ($P = 0.02$) occurred in patients treated with *Avandia* and insulin glargine, respectively. Fifty-seven confirmed hypoglycemic events at plasma glucose < 3.9 mmol/l (< 70 mg/ dl) were identified in patients treated with insulin glargine as compared to forty-seven events in patients treated with *Avandia* ($P = 0.0528$).

6. ADDITIONAL SAFETY INFORMATION

6.1 Interim Analysis of the RECORD Study

RECORD

RECORD (*R*osiglitazone *E*valuated for *C*ardiac *O*utcomes and *R*egulation of glycemia in *D*iabetes), a long-term, randomized, multicenter, open-label, noninferiority study in type 2 diabetes patients, was initiated by GlaxoSmithKline in 2000. [14,117] The study was designed to prospectively compare cardiovascular outcomes in patients with type 2 diabetes treated with *Avandia* plus metformin or sulfonylurea (*Avandia* group) with outcomes in patients treated with metformin plus sulfonylurea (control group).

This study included 4447 type 2 diabetes patients with a HbA1c > 7% and ≤9% despite maximum doses of a sulfonylurea or metformin alone from 338 European and Australian study centers.[14] After a 4 week run-in, patients who were already taking a sulfonylurea were randomly assigned to receive the addition of either *Avandia* (n=1103) or metformin (n=1122). Patients who were already taking metformin were randomly assigned to receive the addition of either *Avandia* (n=1117) or a sulfonylurea (n=1105). The starting dose of *Avandia* was 4 mg/day and the starting doses of metformin and sulfonylurea were determined by local practice. Throughout the study, medications were titrated (following 8 weeks of treatment) to achieve a target HbA1c of ≤ 7%. The maximum daily dose of *Avandia* was 8 mg/day and the maximum dose of metformin was 2550 mg/day. The maximum dose of sulfonylurea was 15 mg/day for glyburide, 240 mg/day for gliclazide, and 4 mg/day for glimepiride. If HbA1c remained ≥ 8.5%, a third oral antidiabetic agent was added in the *Avandia* group or insulin was added in the control group. Patients in the control group (metformin plus sulfonylurea) who started insulin did so according to local practice with or without continuing metformin and/or sulfonylurea. [117] If patients receiving triple therapy in the *Avandia* group had a HbA1c ≥ 8.5%, the study protocol recommended discontinuation of *Avandia* and initiation of insulin. Patients will be followed for approximately 6 years with an anticipated study completion date of late 2008.

The primary endpoint of the study was cardiovascular (CV) hospitalization or death.[14] CV hospitalizations included hospitalization for acute myocardial infarction, congestive heart failure (CHF), stroke, unstable angina, transient ischemic attack, unplanned CV revascularization, amputation of extremities, or any other definite CV reason. CV death included death from CHF, acute myocardial infarction, sudden death, and death caused by acute vascular events such as stroke. Secondary outcomes included all-cause mortality, CHF, combined CV death and/or hospitalization plus microvascular endpoints, all microvascular endpoints, progression of glucose control and need for insulin. [117] An interim analysis of the glycemic control outcomes at 18 months has been published for RECORD.[118] Safety evaluations included monitoring of changes in physical examination, vital signs, laboratory tests, adverse events, and electrocardiograms.

A meta-analysis published in the *New England Journal of Medicine* raised concern regarding the risk of myocardial infarction and CV death associated with *Avandia*. To provide additional information regarding the CV safety of *Avandia*, an unplanned interim analysis was conducted to evaluate the CV outcomes reported so far in the RECORD study. [14] Results of this interim analysis study were published in the *New England Journal of Medicine* on June 5, 2007.

In the RECORD study, there were 2220 patients assigned to receive *Avandia* added to metformin or sulfonylurea (*Avandia* group), and 2227 were assigned to receive a combination of metformin plus a sulfonylurea (control group).[14] The protocol excluded some high-risk patients (i.e. those with CHF, hospitalization for CV causes during the previous 3 months, and pending CV intervention). Baseline characteristics were similar between treatment groups. A total of 140 patients in the *Avandia* group and 244 patients in the control group began to receive insulin. Approximately 10% of patients (218 in the *Avandia* group and 223 in the control group) were lost to follow-up. The interim analysis of RECORD had limited statistical power to detect treatment differences because of the number of patients lost to follow-up, because there was a much lower overall event rate than predicted, and because the mean follow-up was only 3.75 years. Due to the limited power of the interim analysis, a conclusion on the primary endpoint must await the completion of the study.

There was no significant difference between the *Avandia* group and the control group in the adjudicated primary endpoint of CV hospitalization and death. [14] A total of 217 patients in the *Avandia* group and 202 patients in the control group experienced the adjudicated primary endpoint (hazard ratio, 1.08; 95% confidence interval [CI], 0.89 to 1.31). After the inclusion of endpoints for an additional 91 patients (50 in the *Avandia* group and 41 in the control group) pending adjudication, the hazard ratio was 1.11

(95% CI, 0.93 to 1.32). Overall, the rate of the primary endpoint (CV hospitalization or death) was low: 3.1% per year for adjudicated plus pending events.

For the secondary endpoints of myocardial infarction, death from CV or any cause (total mortality), or the composite of CV death, myocardial infarction, and stroke, hereafter referred to as major adverse cardiovascular events (MACE), there was no statistically significant differences between the *Avandia* group and the control group. (14) See Table 26. At this point, the data do not allow a conclusion on the relative risk of myocardial infarction among the medications studied.

Table 26. Hazard Ratios for the Risk of MACE, Myocardial Infarction, and Total Mortality(119)

	MACE		Myocardial Infarction*		Total Mortality	
	n (%)	HR (95% CI)	n (%)	HR (95% CI)	n (%)	HR (95% CI)
RSG + SU or MET N = 2220	93 (4.2)	0.97 (0.73, 1.28)	49 (2.2)	1.09 (0.73, 1.63)	74 (3.3)	0.92 (0.67, 1.26)
SU + MET N = 2227	96 (4.3)		45 (2.0)		80 (3.6)	

* Myocardial infarction or sudden death.
MACE = major adverse cardiovascular events; HR = hazard ratio; CI = confidence interval; RSG = rosiglitazone; SU = sulfonylurea; MET = metformin

Regarding stroke, a post-study ad hoc analysis indicated no statistically significant differences between the *Avandia* group (n = 2220) and the control group (n = 2227) with regard to rate of events per 100 patient-years (0.35 versus 0.46, respectively). (119) The risk of stroke was 24% lower in the *Avandia* group as compared with control (HR 0.76: 0.47-1.23).

Patients in the *Avandia* group had a significantly higher risk of CHF than did patients in the control group, with 38 versus 17 adjudicated events (hazard ratio, 2.24; 95% CI, 1.27 to 3.97). (14) The inclusion of events pending adjudication increased the number of events to 47 and 22, respectively (hazard ratio, 2.15; 95% CI, 1.30 to 3.57), resulting in an excess risk of CHF in the *Avandia* group of 3.0 (95% CI, 1.0 to 5.0) per 1000 patient years of follow-up.

In summary, a significant difference between the *Avandia* and control groups was seen only in the secondary outcome of CHF, where more than twice the number of cases were seen in patients treated with *Avandia*. (14) An independent data safety monitoring board which monitors unblinded safety data twice annually and monitors outcomes throughout the course of the study, has recommended that the RECORD study continue following the interim analysis.

6.2 Interim Results of the ACCORD Trial

ACCORD

The National Heart, Lung, and Blood Institute (NHLBI) of the National Institutes of Health (NIH) has launched the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial.(120) The National Institute on Diabetes and Digestive and Kidney Diseases (NIDDK) is providing additional support for the study. This randomized, open-label, double 2x2 factorial study will assess the effect of intensive glycemic control, lipid control with drug treatment that increases high-density lipoprotein (HDL) and lowers triglycerides (in the context of good lower-density lipoprotein (LDL) control and glycemic control), and intensive blood pressure control (in the context of good glycemic control) on the rate of major cardiovascular (CV) events in 10,000 patients with type 2 diabetes. Classes of glucose-lowering medications available for use include sulfonylureas, biguanides, meglitinides, thiazolidinediones, and insulin. *Avandia* is being provided but investigators have the option of prescribing Actos® (pioglitazone HCl, Takeda Pharmaceuticals America, Inc) at their discretion.

The primary outcome measure is the first occurrence of a major CV disease event (i.e., nonfatal myocardial infarction, nonfatal stroke or CV death). (120) Secondary hypotheses include treatment differences in other CV outcomes, total mortality, microvascular outcomes, health-related quality of life and cost-effectiveness.

Recruitment of 10,251 participants will be treated and followed for approximately 4-8 years at clinical sites located in the US and Canada.

On February 6, 2008, the NHLBI announced it has stopped intensive blood sugar lowering treatment (target HbA1c < 6%) in the study and is transitioning participants in that treatment group to the same goal as participants in the standard treatment group (target HbA1c 7-7.9 %).[121] This change in treatment was due to safety concerns raised during a regular review of the study data by the ACCORD Data and Safety Monitoring Board. An unexpected increase in total deaths from any cause among patients in the intensive blood sugar treatment group compared to those in the standard blood sugar treatment group was identified. The data analyses showed that over an average of almost four years of treatment (approximate range 2-7 years), 257 patients in the intensive-treatment group died, compared with 203 in the standard-treatment group, which is a difference of 54 deaths, or an excess of about 3 deaths per 1,000 patient-years. This translates to a 20% higher rate of death in the intensive group than in the standard group. Investigators for the ACCORD trial have analyzed the available data and have not been able to identify to date any specific cause for the higher death rate among the intensive blood sugar treatment group. Based on analyses done to date, there is no evidence that any medication or combination of medications is responsible for the higher risk. Specifically, investigators reviewed data to determine whether there was any link between *Avandia* and the increased deaths among the intensive blood sugar treatment group. To date, no link has been found.

Interim results from the ACCORD trial were presented at the 68th Annual Scientific Sessions of the American Diabetes Association in San Francisco, CA in June 2008 and published in the *New England Journal of Medicine*.[17] Specifically, the effects of intensive intervention on mortality and the primary composite outcome of major cardiovascular events in all patients and in pre-specified subgroups have been reported. The finding of higher mortality with intensive intervention led to the discontinuation of the intensive therapy group after a mean follow-up of 3.5 years.

In this study, 10,251 type 2 diabetic patients with a mean age of 62.2 years and median HbA1c of 8.1% were randomized to receive intensive therapy (target HbA1c < 6%) or standard therapy (target HbA1c 7-7.9%).[17] Participants between the ages of 40 and 79 with type 2 diabetes and HbA1c ≥ 7.5% with cardiovascular disease or those between the age of 55 and 79 with anatomical evidence of significant atherosclerosis, albuminuria, left ventricular hypertrophy, or at least two additional risk factors for cardiovascular disease (dyslipidemia, hypertension, smoker, or obesity) were randomized for the study. Participants with recent or frequent hypoglycemic events, unwillingness to perform home glucose monitoring or insulin injections, body mass index (BMI) > 45 kg/m^2, serum creatinine > 1.5 mg/dl, or other serous illness were excluded from the study. Of those randomized, ~ 61.5% were male and ~35.2% of participants reported previous cardiovascular event. The average BMI of the study population was 32.2 kg/m^2. Baseline medications included TZD's (~19.4%) , insulin (~34.9%), metformin (~59.9%), sulfonylurea (~50.1%), antihypertensive agents (~85.5%), and statins (~62.1%). Baseline lipid values including total cholesterol, low-density lipoprotein (LDL), high-density lipoprotein (HDL) in men, HDL in women, and median triglycerides were 183.3 mg/dl, 104.9 mg/dl, 38.6 mg/dl, 47.1 mg/dl, and 155 mg/dl, respectively.

At 4 months, the median HbA1c decreased to 6.7% and 7.5% from a baseline of 8.1% in the intensive and standard therapy groups, respectively.[17] A stable median HbA1c of 6.4% and 7.5% was achieved at 1 year in the intensive and standard therapy groups, respectively , and maintained throughout the follow-up period. Compared to standard therapy, participants in the intensive therapy group were associated with a greater exposure to drugs from every class and more frequent changes in number or dose of drug. The glucose lowering regimen was modified by the addition or removal of drug or by increasing or decreasing the dose of an oral agent or insulin a mean of 4.4 times with intensive therapy and 2.2 times with standard therapy.

For the primary composite outcome of nonfatal MI, nonfatal stroke, or death from CV cause, the number of events in the intensive and standard therapy groups were 352 (6.9%) and 371 (7.2%), respectively [HR 0.90; 95% CI, 0.78 to 1.04; P = 0.16].[17] The rate of death from any cause was significantly higher in the intensive therapy group compared with standard therapy (5% vs 4%); [HR 1.22; 95% CI, 1.01 to 1.46; P = 0.04]. Additionally, the rate of death from CV causes was significantly higher with intensive therapy compared to standard therapy (2.6% vs 1.8%); [HR 1.35; 95% CI 1.04 to 1.76; P = 0.02]. Mortality rates in both glycemic control groups were lower than seen in similar populations in epidemiologic studies. The rate of nonfatal MI was significantly lower with intensive therapy compared to standard therapy (3.6% vs 4.6%); [HR 0.76; 95% CI, 0.62 to 0.92; *P* = 0.004].

Compared with standard therapy, the intensive therapy group had significantly higher rates of hypoglycemia, weight gain, and fluid retention.(17) The annualized rate of hypoglycemia requiring medical assistance was 3.1% with intensive therapy and 1% with standard therapy, and mean weight gain was 3.5 kg and 0.4 kg in the two groups, respectively, at 3 years.

It is anticipated that the study will be completed in 2009 with primary results in 2010. (17) Results of the other two treatment strategies being examined in the study (blood pressure and lipid control) remain masked and will continue until 2009.

6.3 Information on VADT

VADT

The Veterans Affairs Diabetes Trial (VADT), coordinated by the Department of Veterans Affairs, Department of Veterans Affairs Cooperative Studies Program, and The American Diabetes Association, was a randomized, open-label, controlled study in 1791 men and women with type 2 diabetes with a median follow-up of 5.6 years. (122) (123) Veterans ≥ 41 years of age who were no longer responsive to daily insulin or maximum doses of oral agents were included in the study. Exclusion criteria included those with an HbA1c of < 7.5%, NYHA functional class III or IV congestive heart failure, cardiovascular events (stroke, myocardial infarction, or revascularization) within the previous 6 months, severe angina, life expectancy of < 7 years, body mass index (BMI) > 40 kg/m^2, serum creatinine > 1.6 mg/dl, or alanine aminotransferase (ALT) > 3 times the upper limit of normal. The majority of subjects were male (97%) and the mean age of the total study population was 60.4 years. The mean duration of diabetes was 11.5 years and baseline HbA1c was 9.4%. More than 40% of participants had prior cardiovascular events, 62% of patients reported prior microvascular complications, 72% had hypertension, and the majority were obese with a mean BMI of 31.3 kg/m^2. At baseline, 52% of patients were receiving insulin.

Patients were randomized to either intensive (HbA1c goal of ≤ 6.0%) or conventional (HbA1c goal of 8-9%) therapy with a goal of 1.5% difference in HbA1c among treatment groups. (123) Both groups received step therapy including metformin (obese patients) or glimepiride (lean patients) plus *Avandia*, and the addition of insulin/other oral agents to reach glycemic goal. Strict control of blood pressure (BP) and dyslipidemia along with daily aspirin therapy, diet and education were identical in both arms of the study.

The primary objective was the time to first occurrence of the composite primary outcome of major macrovascular events (myocardial infarction; stroke; cardiovascular death; new or worsening congestive heart failure; invasive intervention for cardiac, cerebrovascular, or peripheral vascular disease; inoperable coronary disease; and amputation for ischemic diabetic gangrene) with intensive vs. standard glycemic therapy in patients with type 2 diabetes.(122) (123) Secondary objectives assessed differences between treatment groups in other macrovascular endpoints (new or worsening angina, new transient ischemic attacks, new intermittent claudication, new critical limb ischemia or total mortality). Other secondary outcomes included the differences between treatment groups in microvascular complications including retinopathy, nephropathy, and neuropathy.

At 6 months, the median HbA1c decreased to 8.4% and 6.9% from a baseline of 9.4% in the standard and intensive therapy groups, respectively.(122) (123) This corresponded to an absolute between group difference of 1.5 %. For the primary composite outcome, the number of events in the standard and intensive therapy groups were 264 and 235, respectively [hazard ratio (HR) 0.88; 95% confidence interval (CI) 0.74 to 1.05; *P* = 0.14]. Both treatment groups reported fewer events than predicted. Overall, there was no statistically significant difference among treatment groups with regard to the individual components of the primary composite outcome, secondary cardiovascular outcomes, or total mortality. Additionally, there was no statistically significant differences among microvascular complications including retinopathy, major nephropathy, or neuropathy between standard and intensive treatment groups although a nominally significant (*P* = 0.05) reduction in worsening of albumin excretion was observed in the intensive therapy group.

At the end of follow-up, mean BP decreased from a baseline of 132/76 mmHg to 125/69 mmHg and 127/68 mmHg in the standard and intensive treatment groups, respectively.(122) Additionally, all lipid levels (total cholesterol, low density lipoprotein, high density lipoprotein, triglycerides) improved over time in both treatment groups. Overall, there was no significant difference with regard to BP or lipid levels between treatment groups at study end.

Compared to standard therapy, the intensive therapy group had a significantly higher rate of hypoglycemia ($P < 0.001$).(122) Additionally, a greater number of patients in the intensive therapy group had at least one serious adverse event (SAE) compared to standard therapy (24.1% vs 17.6%, respectively; $P = 0.05$). Dyspnea was the most commonly reported SAE in the intensive therapy group ($P = 0.006$). At the end of the follow-up period, weight and BMI were significantly higher in the intensive therapy group (+9 lb and 1.5 kg/m^2, respectively; $P = 0.01$ for both comparisons) compared to standard therapy.

Avandia was the most commonly prescribed drug in the first year of the study, 82% and 78% in the intensive and standard arms, respectively.(124) Time-dependent covariate analyses showed that *Avandia* 4 mg and 8 mg daily were associated with lower risk for the primary composite outcome.(125) The risk analyses included adjustments for age, race, diabetes duration, insulin use, prior CV event, baseline and changes in BP, high-density lipoprotein cholesterol, and HbA1c. A reduction of risk was also demonstrated for CHF and CV death.

7. COMPARATIVE DATA

7.1 Results of the ADOPT Trial

*A D*iabetes *O*utcome *P*rogression *T*rial (ADOPT) was an international, multicenter, randomized, double-blind controlled clinical trial involving 4,360 patients with a median treatment of 4 years.(8) ADOPT was conducted to evaluate the durability of glycemic control in recently diagnosed (<3 years) type 2 diabetes patients receiving *Avandia*, metformin, or glyburide monotherapy. The primary outcome was the time to monotherapy failure, defined as confirmed hyperglycemia when fasting plasma glucose (FPG) > 180 mg/dl on consecutive testing after at least 6 weeks of treatment at the maximal effective or tolerated dose.(8,126) The therapeutic goal was a FPG < 140mg/dl. Fasting plasma glucose values used within the study protocol are consistent with treatment guidelines during the period of study enrollment.

A total of 6,676 patients was screened of which 4,351 were randomized to receive either *Avandia* (n = 1456), metformin (n=1454), or glyburide (n = 1441).(8) Eligible participants randomized for the trial were between the ages of 30 and 75 years, had an FPG that was between 126-180 mg/dl, and had received no prior pharmacologic treatment for their type 2 diabetes; the disease had previously only been managed with diet and exercise. Of those randomized, the majority of participants were male (57.7%), with a mean age and body mass index (BMI) of 56.9 years and 32.2, respectively. Participants with a history of clinically significant hepatic disease, renal impairment, lactic acidosis, unstable or severe angina, congestive heart failure (CHF) New York Heart Association Class I-IV, or uncontrolled hypertension were excluded from participation in the trial.

A placebo run-in of 4 weeks was followed by a median treatment duration of 4 years (maximum 6 years).(8,126) Participants were randomized initially to receive a total daily dose of *Avandia* 4mg, metformin 500mg, or glyburide 2.5mg.(8) During the treatment period, up-titration occurred during each study visit if FPG ≥ 140 mg/dl to a maximum daily dose of *Avandia* 8mg, metformin 2g, and glyburide 15mg. Dose reduction was permitted if study medication was not tolerated. Participants who withdrew from the study prior to completion were given the option to enter a non-treatment observational follow-up.

The primary outcome was the time from randomization to monotherapy treatment failure. Treatment failure was defined as:

- Confirmed hyperglycemia (FPG > 180mg/dl) on consecutive testing after at least 6 weeks of treatment at the maximum tolerated or dictated dose.

An independent adjudication committee used criteria to determine whether the primary outcome had been met in cases where a confirmatory FPG had not been obtained, a patient had withdrawn due to insufficient therapeutic effect, or an additional glucose lowering agent had been administered prior to confirmed hyperglycemia.

Secondary outcomes included time from randomization to a confirmed FPG > 140mg/dl after at least 6 weeks of treatment at the maximum tolerated dose of study medication.

Other prespecified secondary outcomes included:

- FPG
- A1C
- Measures of estimates of insulin sensitivity and β-cell function
- Weight

The primary comparisons within the ADOPT trial were *Avandia* versus metformin and *Avandia* versus glyburide. Secondary analysis was conducted to compare metformin and glyburide.

The cumulative incidence of monotherapy failure at 5 years, according to Kaplan-Meier analysis, was 15% with *Avandia*, 21% with metformin, and 34% with glyburide.[8] This represents a 32% risk reduction in the primary outcome of time to progression to monotherapy failure with *Avandia* as compared with metformin [95% Confidence Interval (CI) 15-45%; $P < 0.001$)], and a 63% risk reduction with *Avandia* as compared with glyburide [95% CI 55-70%; $P < 0.001$]. Additionally, as compared with glyburide, metformin was associated with a 46% risk reduction [95% CI 36-55%, $P < 0.001$] in the primary outcome of time to progression of monotherapy failure. At the time of treatment failure, 99.3 % of participants in the *Avandia* group, 98.6% in the metformin group, and 99.0% in the glyburide group were receiving the maximum dose of study medication. Findings with regard to treatment failure not requiring adjudication remained consistent with those of the primary outcome. A 31% risk reduction in the primary outcome of time to progression to monotherapy failure with *Avandia* as compared with metformin [95% Confidence Interval (CI) 11-46%; $P = 0.004$)], and a 66% risk reduction with *Avandia* as compared with glyburide [95% CI 57-73%; $P < 0.001$] was reported for non-adjudicated treatment failures. Subgroup analyses indicated that *Avandia* was more effective than glyburide in all subgroups while a greater treatment effect was seen with *Avandia* as compared with metformin among older participants (≥ 50 yrs) [*P*-value for heterogeneity = 0.03] and those with larger waist circumference (>110cm) [*P*-value for heterogeneity = 0.01].

There was a 36% risk reduction in the secondary outcome of time to progression to FPG > 140mg/dl with *Avandia* as compared with metformin [79/511 and 127/520, respectively; 95% CI 15-52%; $P = 0.002$] and a 62% risk reduction with *Avandia* as compared with glyburide [79/511 and 160/480, respectively; 95% CI 51-72%; $P < 0.001$]. Additionally, as compared with glyburide, metformin was associated with a 41% risk reduction in time to progression of FPG > 140mg/dl [95% CI 25-54; $P < 0.001$]. Levels of FPG and A1C decreased in all groups within the first 6 months of treatment, however the annual rate of increase in these glycemic parameters was significantly higher in the metformin and glyburide groups as compared with *Avandia* ($P < 0.001$). A 4-year evaluation identified that significantly more participants receiving *Avandia* (40%) had an A1C < 7% as compared with metformin (36%; $P = 0.03$) and glyburide (26%; $P < 0.001$). Mean A1C < 7% was maintained for 57 months with *Avandia*, 45 months with metformin, and 33 months with glyburide.

Estimates of insulin sensitivity and β-cell function were calculated using the homeostasis model assessment (HOMA 2). Insulin sensitivity improved to a greater extent with *Avandia* than with metformin after 6 months of treatment. Thereafter, insulin sensitivity improved at similar rates in the two groups. Insulin sensitivity did not change significantly with glyburide at 4 years. There was a significant improvement in insulin sensitivity with *Avandia* as compared with both metformin (12.6%, 95% CI 8.1-17.3; $P < 0.001$) and glyburide (41.2%, 95% CI 35.2-47.4; $P < 0.001$) at 4 years. β-cell function declined in all treatment groups. The annual rate of decline after 6 months of treatment was significantly less with *Avandia* (-2.0%) as compared with metformin (-3.1%; $P = 0.02$) and glyburide (-6.1%; $P < 0.001$). Mean change in body weight from baseline was +4.8 kg with *Avandia*, -2.9 kg with metformin, and +1.6 kg with glyburide.

Cardiovascular events were reported in 4.3% (n = 62) receiving *Avandia*, 4.0% (n = 58) in the metformin group, and 2.8% (n = 41) in the glyburide group and serious cardiovascular events were reported in 3.4% (n = 49) receiving *Avandia*, 3.2% (n = 46) in the metformin group, and 1.8% (n = 26) in the glyburide group ($P \leq 0.05$ *Avandia* versus glyburide). Additionally, investigator-reported CHF occurred in 1.5% (n = 22), 1.3% (n = 19), and 0.6% (n = 9) of participants receiving *Avandia*, metformin, and glyburide, respectively ($P \leq 0.05$ *Avandia* vs glyburide) and serious investigator-reported CHF occurred in 0.8% (n = 12), 0.8% (n = 12), and 0.2% (n = 3) of participants receiving *Avandia*, metformin, and glyburide, respectively ($P \leq 0.05$ *Avandia* vs glyburide). The hazard ratio for CHF with *Avandia* as compared with metformin was 1.22 (95% CI, 0.66-2.26; $P = 0.52$) and compared with glyburide was 2.20 (95% CI 1.01-4.79; $P = 0.05$). Of the 51 possible CHF events identified by independent cardiology review of all serious adverse events, 21 were confirmed through review and involved 9 participants receiving *Avandia*, 8 receiving metformin, and 4 receiving glyburide (with 1 death).

A post-study ad hoc analysis was conducted to evaluate the ischemic cardiovascular safety events in ADOPT. [9] Results of this analysis are presented in Table 27. The analysis suggests that the risk of myocardial infarction, cardiovascular death, stroke, major adverse cardiovascular events (MACE), and total mortality in patients exposed to *Avandia* was similar to those exposed to either metformin or sulfonylurea.

Table 27. Ischemic Cardiovascular Events in ADOPT[7,9]

Endpoint	Treatment	# of Events	HR(95% CI)*
Myocardial ischemia (Adverse events, non-adjudicated)	SU (n = 1441) Metformin (n = 1454) *Avandia* (n = 1456)	82 111 106	1.18 (0.88-1.57) 0.99 (0.76-1.30)
Myocardial infarction or sudden death † ‡ (Serious adverse events, adjudicated)	SU (n = 1441) Metformin (n = 1454) *Avandia* (n = 1456)	15 17 20	1.20 (0.62-2.35) 1.21 (0.64-2.32)
Stroke‡ (Serious adverse events, non-adjudicated)	SU (n = 1441) Metformin (n = 1454) *Avandia* (n = 1456)	12 17 13	0.94 (0.43-2.07) 0.77 (0.38-1.59)
CV death‡ (Serious adverse events, adjudicated)	SU (n = 1441) Metformin (n = 1454) *Avandia* (n =1456)	12 8 6	0.46 (0.17-1.23) 0.79 (0.27-2.27)
MACE‡ (Serious adverse events, adjudicated MI, sudden death, and CV death, non-adjudicated stroke)	SU (n = 1441) Metformin (n = 1454) *Avandia* (n = 1456)	28 36 35	1.11 (0.67-1.82) 1.00 (0.63-1.59)
Total Mortality‡	SU (n = 1441) Metformin (n = 1454) *Avandia* (n = 1456)	21 15 12	0.51 (0.25, 1.04) 0.82 (0.39, 1.76)

HR = hazard ratio; CI = confidence interval; SU = sulfonylurea; MACE = major adverse cardiovascular event [MACE components include serious adverse events for: CV death, myocardial infarction (definite or unconfirmed) or sudden death, and stroke]

* Statistically, a hazard ratio of 1 means no difference in risk between the two agents being compared. If the confidence interval for a hazard ratio includes 1.0, there is no statistically significant difference between the rates compared. If the confidence interval for a hazard ratio does not include 1.0, that result is deemed statistically significant. † Myocardial infarction includes events adjudicated as definite or unconfirmed; ‡ Post-study ad hoc analysis

Edema was reported in 14.1% of participants receiving *Avandia*, 7.2% of participants receiving metformin, and 8.5% of participants receiving glyburide ($P \leq 0.01$ *Avandia* vs glyburide and vs metformin). Gastrointestinal events were less frequently reported with *Avandia* (23%) as compared to metformin (38.3%; $P \leq 0.01$). Hypoglycemia was less frequently reported with *Avandia* (9.8%) than metformin (11.6%) and glyburide (38.7%; $P \leq 0.01$). Mean alanine aminotransferase (ALT) levels decreased significantly in participants receiving *Avandia* as compared with both metformin and glyburide ($P \leq 0.01$). Low-density-lipoprotein (LDL) levels were significantly higher with *Avandia* (104 mg/dl) as compared to both metformin (96.5 mg/dl) and glyburide (99.3 mg/dl; $P \leq 0.01$).

At the time the original article was being published, further examination of the data on adverse events identified an unexpected event not part of the prespecified analysis plan. A note added in proof indicated that there was a higher incidence of fractures in patients receiving *Avandia*. There was a significantly higher incidence of fractures observed in women receiving *Avandia* as compared with either metformin or glyburide (9.3%, 5.1%, and 3.5%, respectively; $P < 0.01$). The number of men with fractures did not differ according to treatment group (4.0% with *Avandia*, 3.4% with metformin, and 3.4% with glyburide). The frequency of upper limb fractures was significantly higher in women receiving *Avandia* (3.4%) as compared with glyburide (1.5%; $P < 0.05$) while the frequency of lower limb fractures was significantly higher with *Avandia* (5.6%) as compared to both metformin (3.1%; $P < 0.05$) and glyburide (1.3%; $P < 0.01$). Upper limb fractures were reported to involve primarily the humerus and the hand while lower limb fractures involved primarily the foot. The number of women with hip fractures did not differ with *Avandia* and metformin (2 patients receiving *Avandia*, 2 receiving metformin, and none receiving glyburide). Fracture observations are under further evaluation.

7.2 The Risk of Myocardial Ischemic Events with *Avandia* Compared to Actos

Limitations of Observational Studies

Although randomized, controlled trials are generally considered to be the best method of assessing risk, observational studies are often used to address research questions.(127) Observational studies are an important source of data to address safety related questions as they evaluate large populations of diverse individuals in a real world setting. However, observational studies can be vulnerable to methodological problems.(127,128) When evaluating observational studies, it is important to assess all possible reasons for an association including bias, confounding, chance, as well as cause.(127)

Randomized, controlled clinical trials specifically designed to evaluate the differences in the risk of myocardial ischemic events between *Avandia* and pioglitazone have not been conducted.

Background

Statistically, a hazard ratio (HR) of 1 means no difference in risk between the two agents being compared. If the confidence interval for a HR includes 1.0, there is no statistically significant difference between the rates compared. If the confidence interval for a HR does not include 1.0, that result is deemed statistically significant.

Pharmetrics Study(129,130)

An observational study was commissioned by GSK, which analyzed 402,845 patients with type 2 diabetes, using the PharMetrics Patient-Centric database, including a head-to head comparison of *Avandia* (n = 57,381) to pioglitazone (n = 51, 641). The database consists of automated claims patient data that have been aggregated from over 80 managed care databases in the United States. Between July 2000 and March 2007, new users of specific anti-diabetic regimens were identified and classified into monotherapy with *Avandia*, pioglitazone, metformin, or sulfonylurea, dual therapy with any 2 of these agents, or the use of any of these agents or other oral anti-diabetic drugs in combination with insulin. The primary outcome of the study was the first occurrence of myocardial infarction (MI) or coronary revascularization (CR). Hospital discharge diagnoses from insurance claims were used to identify new cases of MI or CR during follow-up. The average follow-up ranged from 12 to 18 months across the different cohorts. Relative risks for pair wise head-to-head comparisons within monotherapy, dual therapy, and combination with insulin cohorts were calculated using a stratified Cox-proportional hazards model, with 10 strata created from the central 90 percent of the propensity scores appropriate to each pair.

In the monotherapy cohorts, the number of patients receiving *Avandia*, pioglitazone, metformin, and sulfonylureas was 12,440, 16,302, 131,075, and 48,376, respectively. For the composite outcome of MI and/or CR, the hazard ratio (HR) for *Avandia* versus pioglitazone was 0.97 [95% confidence interval (CI): 0.78-1.20], indicating no statistically significant difference between these thiazolidinediones. Additionally, for MI alone, the HR for *Avandia* versus pioglitazone was 0.78 (95% CI: 0.52-1.18).

In the dual therapy cohorts, 36,906 patients were receiving *Avandia* in combination with metformin or sulfonylurea and 27,415 patients were receiving pioglitazone in combination with metformin or sulfonylurea. Outcome rates for the composite of MI and/or CR in patients receiving *Avandia* versus those receiving pioglitazone were similar in combination with both metformin (HR 0.97, 95% CI: 0.81-1.17) and sulfonylureas (HR 1.12, 95% CI: 0.89-1.41). Additionally, for MI alone, the outcome rates in patients receiving *Avandia* versus those receiving pioglitazone were similar in combination with both metformin (HR 1.01, 95% CI: 0.71-1.44) and sulfonylureas (HR 1.22, 95% CI: 0.83-1.78).

In the combination-with-insulin cohorts, 8,035 and 7,924 patients were receiving *Avandia* and pioglitazone, respectively. In these two groups, the risk of the composite outcome of MI and/or CR and MI alone were similar (HR 1.07 95% CI: 0.89-1.29 and HR 1.02 95% CI: 0.75-1.39, respectively).

The overall hazard ratios for the composite outcome of MI and/or CR and its individual components of MI or CR comparing all *Avandia* regimens to all pioglitazone regimens are provided in Table 28. The risk of MI, CR, and the composite outcome of MI and CR was similar between *Avandia* and pioglitazone.

Table 28. Hazard Ratio of Composite and Individual Outcomes: *Avandia* regimens vs. Pioglitazone regimens[130]

	HR	**95% CI**
MI	1.07	0.89-1.27
CR	1.03	0.93-1.14
Composite outcome: MI and CR	1.04	0.94-1.14

MI = myocardial infarction; CR = coronary revascularization; HR = hazard ratio; CI = confidence interval

There are several limitations with regard to this analysis. In considering crude incidence rates, it is important to note that sulfonylurea initiators were generally older compared to metformin initiators, which included a relative preponderance of subjects under the age of 35. These younger patients also had fewer comorbid conditions and baseline cardiovascular risk factors. Initiators of *Avandia* and pioglitazone were more similar to one another in patient characteristics than patients on other regimens. Pioglitazone initiators had a higher prevalence of baseline hyperlipidemia than did *Avandia* initiators (48.3% for pioglitazone monotherapy compared to 42.5% for *Avandia* monotherapy). However, this difference was adjusted by including hyperlipidemia in the propensity score.

Ingenix Study[131]

A retrospective cohort study was conducted by Takeda Pharmaceutical Company Limited using the Ingenix database to analyze patients who initiated *Avandia* or pioglitazone between 2003-2006. The objective of this study was to compare the risk of hospitalization for acute MI in type 2 diabetes patients treated with pioglitazone relative to *Avandia*. The primary and secondary outcomes of hospitalization for acute MI, and composite of acute MI or CR were evaluated using hospital discharge diagnosis ICD-9 coding. The HR of incident hospitalization for acute MI and for the composite endpoint of acute MI or CR, in patients using pioglitazone compared to *Avandia* was estimated from multivariate Cox's proportional hazards survival analysis. Several baseline variables were considered potential risk factors for MI and were introduced into the statistical model as covariates including: age, gender, duration of diabetes drug treatment, year of index drug initiation, medical conditions and procedures such as hypertension, prior MI, prior CR, angina, unstable angina, coronary heart disease, congestive heart failure, hyperlipidemia, smoking, obesity, arrhythmias, and stroke, and dispensed drugs including metformin, sulfonylurea, meglitinides, insulin, other anti-diabetic agents, nitrates, beta-blockers, calcium-channel blockers, diuretics, angiotensin-converting enzyme (ACE)-inhibitors, angiotensin-receptor blockers, statins, fibrates, aspirin, non-steriodal antiinflammatory drugs, antiplatelet agents, and anticoagulants.

In total, 29,911 patients were included in the study with 14,807 in the pioglitazone group and 15,104 in the *Avandia* group. The groups were generally well balanced at baseline; however, the use of statins and fibrates was higher in patients receiving pioglitazone as compared with *Avandia* (statins: 39.9% vs. 34.7% and fibrates: 10.1% vs. 8.0%). Additionally, more patients in the *Avandia* group were receiving metformin (55.2% vs. 41.6%) as compared to pioglitazone. In the pioglitazone and *Avandia* groups, the average follow-up time was 1.2 years and 1.3 years, respectively.

In the group receiving pioglitazone, 161 (1.1%) patients were hospitalized for acute MI, which constitutes an unadjusted incidence rate of 93.3 (95% CI: 80.0-108.8) per 10,000 patient-years. In the *Avandia* group, 214 (1.4%) patients were hospitalized for acute MI, constituting an unadjusted incidence rate of 111.3 (95% CI: 97.0-127.1) per 10,000 patient years. The unadjusted HR for hospitalization for acute MI for pioglitazone relative to *Avandia* was 0.82 (95% CI: 0.67-1.01), indicating no statistically significant difference between the groups, and 0.78 (95% CI: 0.63-0.96) after adjusting for the baseline covariates described above. There were 386 (2.6%) patients in the pioglitazone group and 468 (3.1%) in the *Avandia* group with a first event in the composite endpoint of acute MI or CR. The adjusted HR was 0.85 (95% CI: 0.75-0.98).

To assess the differences in baseline use of metformin and lipid lowering agents, sensitivity analyses were conducted. The HR for patients in the pioglitazone group relative to the *Avandia* group who were receiving metformin at baseline was 0.85 (95% CI: 0.62-1.19), while the HR was 0.74 (95% CI: 0.56-0.97) for those who were not receiving metformin. Among patients who were receiving statins or fibrates at baseline, the HR for acute MI was 0.59 (95% CI: 0.43-0.81). However, among patients who were not taking these agents at baseline, there was no difference in acute MI between the pioglitazone and *Avandia* groups [HR 0.96 (95% CI: 0.73-1.26)].

Several aspects of this study create potential bias. The use of lipid lowering agents is known to help reduce the risk of MI, and in this study, the use of statins and fibrates was higher in the pioglitazone group compared to the *Avandia* group. In addition, the study does not distinguish between results for patients taking pioglitazone and *Avandia* as monotherapy, dual therapy, and combinations with insulin. Therefore, the mix of therapies was unknown between the groups. Patients on combination therapy may have more progressive disease and may be at a greater risk of events. A difference in the distribution of monotherapy, dual therapy, and combination therapy with insulin between the groups may have contributed to the difference in outcomes between pioglitazone and *Avandia*.

Wellpoint Cohort Study

A retrospective-longitudinal cohort study was conducted by HealthCore, the health outcomes research subsidiary of WellPoint.(132) WellPoint is a health benefits company providing health coverage to over 34 million Americans. This study was entirely funded by WellPoint and conducted to determine if there is evidence in a real world setting of elevated risk of myocardial infarction (MI) in patients receiving *Avandia* or pioglitazone. The primary objective was to determine the risk of acute MI in patients taking *Avandia* or pioglitazone compared to patients taking other oral antidiabetic agents (OADs). Details of this study are limited to what was presented at the Joint Meeting of the Endocrinologic and Metabolic Drugs Advisory Committee on July 30, 2007.

The study used integrated health claims data including pharmacy, medical, and member eligibility for five of WellPoint's plans from January 1, 2001 through December 31, 2006. The *Avandia* cohort included patients taking *Avandia* as monotherapy or in combination with other OADs. Similarly, the pioglitazone cohort included patients taking pioglitazone as monotherapy or in combination with other OADs. Subjects taking insulin or both TZD's during the evaluation period were excluded. Acute MI was determined by review of all medical claims for care in the hospital or emergency room using ICD-9 codes (410.XX). As part of the sensitivity analysis, the definition of acute MI was expanded to include unstable angina (ICD-9 code 411.1X). The severity of illness, complications and intensity of diabetes were determined by evaluation of covariates including markers of cardiovascular (CV) risk in the year prior to initiating therapy.

Multivariate Cox-proportional hazards modeling was used to evaluate the independent effects of exposure to *Avandia*, pioglitazone, and other OADs on the risk of acute MI. Baseline CV risk factors were adjusted for using the CV risk score. In addition, extensive sensitivity analyses were conducted to assess the impact of definition of outcome and exposures.

The study sample included 22,050 users of *Avandia*, 23,768 users of pioglitazone, and 120,771 users of other OADs. Patients taking *Avandia* and pioglitazone were significantly older and had a higher burden of comorbidities than patients taking all other OADs. Patients taking *Avandia* and pioglitazone had a significantly higher pre-index CV disease and CV medication utilization. A statistically significant greater use of angiotensin-receptor blockers, beta-blockers, calcium-channel blockers and lipid-altering medications was observed in the pioglitazone cohort compared to the *Avandia* cohort ($P < 0.05$ for each medication). Both *Avandia* and pioglitazone patients had almost twice the diabetic hospitalizations and a greater burden of complications including retinopathy and nephropathy compared to patients treated with OADs prior to treatment.

The number of incident acute MIs excluding angina was 212 for *Avandia* , 232 for pioglitazone, and 866 for other OADs. The incidence rates of acute MI were 0.73, 0.74, and 0.72 per 100 patient years for *Avandia*, pioglitazone, and other OADs, respectively. When angina was included, the incidence rates were 1.43, 1.33, and 1.34 per 100 patient years, respectively as above. The adjusted hazard ratio (HR) for acute MI for patients treated with *Avandia* compared to other OADs was 1.029 (P = 0.710) and 1.044 (P = 0.553) in patients treated with pioglitazone (Table 29).

Table 29. Adjusted Hazard Ratios of Acute MI including and Excluding Unstable Angina for Avandia, Pioglitazone and Other OADs[132]

	Acute MI = 410.XX (ICD-9 code)			Acute MI = 410.XX or 411.1X		
	HR	**95% CI**	**P- value**	**HR**	**95% CI**	***P*- value**
Avandia	1.029	0.886-1.194	0.710	1.086	0.979-1.205	0.117
Pioglitazone	1.044	0.905-1.205	0.553	0.987	0.890-1.095	0.808
OADs	reference	reference	reference	reference	reference	reference
CI = Confidence interval; HR = Hazard ratio; MI = Myocardial infarction; OADs = Oral antidiabetic agents						

Compared to oral antidiabetic agents, the adjusted HR for acute MI excluding angina for monotherapy cohorts (almost 6,000 for *Avandia* and 9,000 for pioglitazone) was 0.977 in patients taking *Avandia* and 0.861 in patients taking pioglitazone, neither one was statistically significant (Table 30).

Table 30. Adjusted Hazards Ratios of Acute MI including and Excluding Unstable Angina in Monotherapy Cohorts for *Avandia*, Pioglitazone, and Other Oral Antidiabetic Agents[132]

	Acute MI = 410.XX (ICD-9 code)			Acute MI = 410.XX or 411.1X		
	HR	**95% CI**	***P*- value**	**HR**	**95% CI**	***P*-value**
Avandia	0.977	0.734 – 1.301	0.874	1.159	0.963 – 1.395	0.118
Pioglitazone	0.861	0.610 – 1.216	0.396	0.912	0.720 - 1.155	0.445
Other OADs	reference	reference	reference	reference	reference	reference
CI = Confidence interval; HR = Hazard ratio; MI = Myocardial infarction; OADs = Oral antidiabetic agents						

When the analysis was limited to that of drug treatment period, the HR for acute MI was 0.945 for *Avandia* and 0.90 for pioglitazone with no statistical significance (Table 31).

Table 31. Adjusted HR of Acute MI Including and Excluding Unstable Angina for *Avandia*, Pioglitazone, and Other Oral Antidiabetic Agents Limited to Treatment Period[132]

	Acute MI = 410.XX (ICD-9 code)			Acute MI = 410.XX or 411.1X		
	HR	**95% CI**	***P*- value**	**HR**	**95% CI**	***P*-value**
Avandia	0.945	0.656 – 1.362	0.762	0.959	0.764 – 1.203	0.718
Pioglitazone	0.900	0.633 – 1.278	0.555	0.811	0.646 - 1.020	0.073
Other OADs	reference	reference	reference	reference	reference	reference
CI = Confidence interval; HR = Hazard ratio; MI = Myocardial infarction; OADs = Oral antidiabetic agents						

The WellPoint investigators reported that they did not identify a statistically significant increase in the risk for acute cardiac events, including MI and unstable angina, in patients who received *Avandia* or pioglitazone when compared to patients taking other oral anti-diabetic agents.[132] In addition, a sub-cohort of patients treated with *Avandia* or pioglitazone as monotherapy were also found to not have an elevated risk of acute cardiac events.

Tricare Study[133,134]

The Department of Defense conducted a cross-sectional analysis of data from fiscal years 2003-2006 to determine if there was an increased incidence of acute MI and CHF among Military Health System (MHS) beneficiaries who filled a prescription for *Avandia* compared to those who filled a prescription for other antidiabetic medications. The MHS provides health coverage to approximately 9.1 million beneficiaries. The data for the analysis was collected from enrollees of TRICARE Prime, which is a managed care option similar to a civilian health maintenance organization. The study was limited to individuals younger than 65 years of age since older individuals are not eligible for TRICARE Prime. This information was presented at the Joint Meeting of the Endocrinologic and Metabolic Drugs Advisory Committee on July 30, 2007 and recently published in the *American Journal of Therapeutics*.

The analysis used three different data sources: Defense Eligibility Enrollment System (DEERS), inpatient/outpatient encounter claims, and Pharmacy Data Transaction Service (PDTS). DEERS provided data necessary for the establishment of demographic characteristics of the population. The inpatient/outpatient encounter claims included the date and source of service received, diagnoses of diseases according to ICD-9 and procedure codes (DRG). PDTS allowed tracking of the real time prescription fill records regardless of sources of fill. The three data sources were linked by identifiers.

Type 2 diabetes was defined using the ICD-9 code. Individual drugs were grouped into therapeutic classes of antidiabetic drugs. The drug categories defined were not mutually exclusive, and therefore, statistical comparisons of the drugs analyzed were not preformed. Incident cases of acute MI and CHF were identified using the earliest date of diagnosis.

In total, 231,962 diabetic patients were included in the study of which 46% were male and 54% were female. Approximately 70% of the individuals in the study were between 45 and 64 years of age.Table 32 provides the annual incidence rates of acute MI averaged over the 4 year period of the study.

Table 32. Annual Incidence Rates of Acute Myocardial Infarction Averaged Over the 4 Year Period in TRICARE Prime (2003-2006) [133,134]

		Acute MI	
	N Dispensed Drug	N	Average Annual Incidence per 10,000
Any TZD	20,002	299	37.37
Avandia	13,400	202	37.69
Pioglitazone	7,831	111	35.44
Biguanides	58,091	769	33.09
Sulfonylureas	23,520	457	48.58
Insulin	11,854	245	51.67
Nitrates	6561	831	316.64
Avandia + nitrates	1320	177	335.23
Pioglitazone + nitrates	891	131	367.56

The authors concluded that there was no increased annual incidence of acute MI among TRICARE Prime beneficiaries with a diagnosis of type 2 diabetes who have filled a prescription for *Avandia* compared with those who filled prescriptions for other antidiabetic medications.

There were several limitations to this study. The study did not adjust for potential confounding factors such as socioeconomic status, comorbid conditions, current health status, medical history, drug dose, time on drug, concurrent medications, or individual characteristics such as body mass index, diet, smoking, and exercise. Therefore, it was not possible to determine whether the observed differences in average annual incidence rates of the outcomes were due to the inherent differences in antidiabetic drugs or other confounding factors such as disease progression, other risk factors for cardiovascular events such as age, and the differences in the number, type, and severity of comorbid conditions. The study also did not include individuals who were 65 years of age and older. The outcome of acute MI was attributed to the antidiabetic class if the prescription was filled at any time prior to the event, assuming a cause-effect relationship. An additional limitation was that the drug categories were not mutually exclusive and therefore statistical comparisons for significance were not possible.

Integrated Healthcare Information Services (IHCIS) Study[135,136]

An observational study was conducted using the Integrated Healthcare Information Services (IHCIS) database, a U.S. managed care claims database which contains data on 891,901 patients with type 2 diabetes. The study was a case-control analysis nested within the cohort of eligible type 2 diabetic patients captured in IHCIS from 1999-2006. The study was designed to determine the odds of MI in patients with type 2 diabetes exposed to thiazolidinediones (TZDs) (*Avandia* and pioglitazone, separately) compared to those exposed to other anti-diabetic agents. Incident cases of hospitalization for MI were identified among type 2 diabetic patients. Three controls were matched to each case based on age (+/- 5 years), gender, calendar year of diabetes diagnosis, and year of MI diagnosis (index year). The odds of MI were modeled using conditional logistic regression, adjusting for age, gender, ACE-inhibitor use, beta-blocker use, diuretic use, nitrate use, and hyperlipidemia and hypertension diagnosis.

The incidence rate of MI in the diabetic cohort was 5.25 per 1,000 person-years (95% CI: 5.15-5.36). The average follow-up was 2.1 years, during which 9,870 MI cases (1.1%) were identified and matched to 29,610 controls. In the 3 months prior to the index date (recent exposure), 1,149 (11.6%) cases and 2,690 (9.1%) controls were exposed to *Avandia*, 910 (9.2%) cases and 2,433 (8.2%) controls were exposed to pioglitazone, and 5,644 (57.2%) cases and 13,702 (46.3%) controls were treated with other anti-diabetic therapies excluding TZDs. The risk of MI in patients exposed to either *Avandia* or pioglitazone compared with those patients exposed to other anti-diabetic therapies was 1.03 (95% CI: 0.99-1.12) and 0.92 (95% CI: 0.83-1.01), respectively. The risk of MI in subjects exposed to *Avandia* or pioglitazone for ≤ 12 months is not different from those exposed to other antidiabetic agents but exposure for >12 months is associated with a 15% and 13% increased risk of MI, respectively.

A limitation to this analysis is the utilization of a nested-case control study design. Results of cohort studies utilizing propensity scores represent a higher level of study design and evidence.

Institute for Clinical Evaluative Sciences (ICES) Study[57]

A population-based, retrospective nested case-control cohort study was conducted using health care databases from Ontario, Canada to evaluate the risks of congestive heart failure (CHF), acute MI, and all-cause mortality associated with the use of TZDs compared to other oral hypoglycemic drug combination therapies. Of note, reimbursement for TZDs during the time of the study was restricted to patients experiencing uncontrolled hyperglycemia or to those who had a contraindication or intolerance to metformin and/or sulfonylureas. The study population included diabetic patients from Ontario who were 66 years of age or older treated with at least 1 oral hypoglycemic drug between April 1, 2002 and March 31, 2005. Patients who were treated with insulin in the year prior to cohort entry were excluded, while patients who began treatment with insulin during follow-up were retained in the study. Patients were followed up until they experienced an event, death, a last health services contact in Ontario (for those who lost health contact for at least 6 months), or March 31, 2006, whichever occurred first. The primary outcome of the study was a first hospital visit for CHF defined as an emergency room visit for CHF or a hospital admission with CHF as the discharge diagnosis. The secondary study outcomes were a hospital visit for acute MI, defined as either an emergency room visit for MI or a hospital admission with MI as the discharge diagnosis, and all-cause mortality.

The study population consisted of 159,026 diabetic patients who were treated with oral hypoglycemic agents. The mean age of the individuals included in the study was 74.7 years, and the median follow-up for the study was 3.8 years. A greater proportion of patients taking TZD monotherapy had a history of renal and cardiovascular disease compared with those receiving TZD combination therapy and other oral antidiabetic agent combination therapy. Patients receiving *Avandia* monotherapy had greater comorbidity compared with those prescribed pioglitazone monotherapy, although the proportion with a history of cardiovascular disease was similar. All other baseline characteristics were similar between the groups. Cases and controls were well matched for age, sex, cardiovascular history, and duration of diabetes; however, the occurrence of noncardiac comorbidity was somewhat higher among cases than controls.

Overall, 7.9% of patients (n = 12,491) had a hospital visit for CHF, 7.9% for acute MI (n = 12,578), and 19% died (n = 30,265). Compared with patients receiving other oral hypoglycemic agent combination therapy, current users of TZD monotherapy and combination therapy were at an increased risk of CHF and death. An increased risk of acute MI was seen with current use of TZD monotherapy, but not TZD combination therapy, compared to use of other oral hypoglycemic agent combinations. The association between CHF, acute MI, and mortality and TZD therapy appeared to be limited to treatment with *Avandia*; however, there was limited power to explore the association between outcomes and the use of pioglitazone due to the smaller number of patients taking pioglitazone. Table 33 summarizes the results for acute MI and mortality.

Table 33. Rate Ratios of Acute Myocardial Infarction and All-Cause Mortality With the Use of Thiazolidinediones Compared to Other Oral Hypoglycemic Agent Combination Therapies[57]

	Number of Cases	**Number of Controls**	**Unadjusted Rate Ratio (95% Confidence Interval)***	**Adjusted Rate Ratio (95% Confidence Interval)*†**	***P* Value for Adjusted Rate Ratio**
Acute Myocardial Infarction					
Current Other OHA Combination Therapy‡	3695	18351			
Current TZD monotherapy§	65	228	1.42 (1.08-1.88)	1.40 (1.05-1.86)	0.02
Avandia	53	147	1.80 (1.31-2.46)	1.76 (1.27-2.44)	<0.001
Pioglitazone	12	81	0.74 (0.41-1.37)	0.73 (0.40-1.36)	0.33
Current TZD Combination Therapy	404	2109	0.96 (0.86-1.07)	0.96 (0.85-1.08)	0.49
Avandia	282	1404	1.00 (0.88-1.15)	1.00 (0.87-1.16)	0.96
Pioglitazone	122	705	0.87 (0.72-1.06)	0.87 (0.71-1.06)	0.17
Past Treatment with TZDs‖	140	630	1.11 (0.92-1.34)	1.05 (0.87-1.28)	0.62
Avandia	95	424	1.12 (0.90-1.41)	1.06 (0.84-1.34)	0.65
Pioglitazone	45	206	1.10 (0.79-1.52)	1.04 (0.75-1.45)	0.81
All-Cause Mortality					
Current Other OHA Combination Therapy‡	5529	18835			

OHA - Oral hypoglycemic agent; TZD - Thiazolidinedione

*All models were also adjusted for current insulin combination therapy (cases = 370; controls = 1084), insulin monotherapy (cases = 361; controls = 1010), other OHA monotherapy (cases = 7667; controls = 40108), and no current therapy (cases = 1803; controls = 8400).

†Adjusted for income quintile; residence in long-term care facility; Charlson comorbidity score category; history of use of angiotensin-converting enzyme inhibitors, nonsteroidal anti-inflammatory drugs, β-blockers, calcium channel blockers, diuretics, spironolactone, statins, and digoxin; prior metformin use; prior sulfonylurea use; prior use of other OHAs; prior use of TZDs; congestive heart failure in past year and in past 1-5 years; angina in past year and in past 1-5 years; coronary artery bypass graft surgery in past year and in past 1-5 years; coronary catheterization in past year and in past 1-5 years; percutaneous transluminal coronary angioplasty in past year and in past 1-5 years; history of renal disease; and number of drugs prescribed in prior 6 months.

‡Other than TZDs; more than 97% were receiving metformin + sulfonylurea.

§Current users are those who were dispensed the drug with the days supplied overlapping the index date by 14 days or more.

‖Past users are those who were dispensed the drug with the days supplied ending between 15 and 365 days before the index date.

	Number of Cases	Number of Controls	Unadjusted Rate Ratio (95% Confidence Interval)*	Adjusted Rate Ratio (95% Confidence Interval)*†	*P* Value for Adjusted Rate Ratio
Current TZD monotherapy§	102	392	0.85 (0.68-1.06)	1.29 (1.02-1.62)	0.03
Avandia	76	255	0.99 (0.76-1.29)	1.47 (1.12-1.93)	0.005
Pioglitazone	26	137	0.60 (0.39-0.91)	0.94 (0.61-1.45)	0.78
Current TZD Combination Therapy	497	1440	1.17 (1.05-1.30)	1.24 (1.11-1.39)	<0.001
Avandia	358	1027	1.18 (1.04-1.34)	1.26 (1.10-1.44)	<0.001
Pioglitazone	139	413	1.15 (0.94-1.40)	1.20 (0.98-1.47)	0.08
Past Treatment with TZDs‖	458	807	1.93 (1.71-2.18)	2.08 (1.82-2.37)	<0.001
Avandia	314	576	1.85 (1.61-2.14)	1.98 (1.70-2.31)	<0.001
Pioglitazone	144	231	2.14 (1.73-2.65)	2.32 (1.85-2.90)	<0.001

OHA - Oral hypoglycemic agent; TZD - Thiazolidinedione

*All models were also adjusted for current insulin combination therapy (cases = 370; controls = 1084), insulin monotherapy (cases = 361; controls = 1010), other OHA monotherapy (cases = 7667; controls = 40108), and no current therapy (cases = 1803; controls = 8400).

†Adjusted for income quintile; residence in long-term care facility; Charlson comorbidity score category; history of use of angiotensin-converting enzyme inhibitors, nonsteroidal anti-inflammatory drugs, β-blockers, calcium channel blockers, diuretics, spironolactone, statins, and digoxin; prior metformin use; prior sulfonylurea use; prior use of other OHAs; prior use of TZDs; congestive heart failure in past year and in past 1-5 years; angina in past year and in past 1-5 years; coronary artery bypass graft surgery in past year and in past 1-5 years; coronary catheterization in past year and in past 1-5 years; percutaneous transluminal coronary angioplasty in past year and in past 1-5 years; history of renal disease; and number of drugs prescribed in prior 6 months.

‡Other than TZDs; more than 97% were receiving metformin + sulfonylurea.

§Current users are those who were dispensed the drug with the days supplied overlapping the index date by 14 days or more.

‖Past users are those who were dispensed the drug with the days supplied ending between 15 and 365 days before the index date.

This study contains significant limitations which could have biased the results. The database used in this study is composed of a select group of patients. During the study, TZDs were restricted to those patients who failed treatment on metformin and sulfonylurea or for whom sulfonylurea or metformin were contraindicated. Therefore, TZD patients had a higher baseline risk for cardiovascular disease, and the use of TZDs in this database does not reflect the real world use. Patients who were prescribed *Avandia* monotherapy suffered from more chronic diseases compared with those prescribed pioglitazone monotherapy, and therefore, were sicker patients. This difference is not corrected for in the analysis of the data and in the study conclusions. In addition, the TZD monotherapy group had a 3 to 4-fold higher rate of renal impairment, which is indicative of patients with more progressive type 2 diabetes. Furthermore, the authors state that the study may have been underpowered to detect adverse effects associated with pioglitazone due to the relatively small number of patients prescribed this agent. It is stated that larger studies are needed to better determine the relative effect of each agent on cardiovascular outcomes.

An Innapropriate Comparison Between Meta-analyses

Two meta-analyses were published side by side in the September 12, 2007 edition of the Journal of the American Medical Association (JAMA). One meta-analysis conducted by Singh, et al, assessed the long-term risk of cardiovascular events with *Avandia*, utilizing the endpoints of myocardial infarction, heart failure, and cardiovascular mortality.(137) In this analysis the relative risk (RR) for MI for *Avandia* (n = 94/6421) compared to control (n = 83/7870) was 1.42 (95% CI: 1.06-1.91; *P* = 0.02). The RR of heart failure with *Avandia* (n = 102/6421) compared to control (n = 62/7870) was 2.09 (95% CI: 1.52-2.88; *P*<0.001). There was no significant risk of cardiovascular mortality with *Avandia* (n = 59/6421) compared to control (n = 72/7870) (RR 0.90; 95% CI: 0.63-1.26; *P* = 0.53). The other meta-analysis conducted by Lincoff et al, evaluated a composite endpoint of death, myocardial infarction, or stroke in patients treated with pioglitazone.(138) The composite endpoint occurred in 4.4% (n = 375/8554) of patients receiving pioglitazone and 5.7% (n = 450/7836) of patients receiving control therapy (HR 0.82; 95% CI: 0.72-0.94; *P* = 0.005).

These articles appear to be written and published in a manner meant to draw comparisons between *Avandia* and pioglitazone that cannot be made for many reasons, including:

• Each meta-analysis used a set of clinical trials that studied different populations, some studying drug-naïve patients, while others studied patients on insulin or with documented histories of cardiovascular events

• The endpoints used in each of the trials, and each of the meta-analyses were different

• The duration, event rate, analysis method, and event definitions varied across trials

The pioglitzone meta-analysis is based on a small number of studies (19), and is heavily influenced by data from the PROactive study (5,238 patients) which contributed 32% of the entire population of the meta-analysis and 55% of the patient-years.(138) PROactive compared diabetic patients who were randomly assigned to pioglitazone or placebo in addition to their existing antidiabetic medications.(139)

No statistical difference between *Avandia* and comparators was observed when the endpoint of CV death, myocardial infarction and stroke are applied to the data on *Avandia* , across long-term clinical trials (HR 1.03).(140) In RECORD, a study specifically designed to look at cardiovascular events, no appreciable difference was seen between *Avandia* and comparators (HR 0.96).(14) These results are similar to the results from the meta-analysis conducted by Lincoff et al , which observed HR 0.82 in patients treated with pioglitazone.(138)

There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with *Avandia* or any other oral antidiabetic drug.(7)

7.3 Comparison of the Lipid Profile of *Avandia* and Pioglitazone in Type 2 Diabetes Patients

The lipid and glycemic effects of *Avandia* and pioglitazone were compared in a 24-week, randomized, double-blind study in patients with type 2 diabetes (treated with diet alone or oral monotherapy) and dyslipidemia (triglycerides [TG] ≥ 150 mg/dL and < 600 mg/dL and fasting low-density lipoprotein [LDL] < 130 mg/dL). (141) Patients were excluded from the study if they received any lipid-lowering agents within 60 days of screening. Following a 4-week placebo washout period, patients were randomized to receive either *Avandia* 4 mg once daily or pioglitazone 30 mg once daily for 12 weeks. For the final 12 weeks, doses of *Avandia* and pioglitazone were increased to 4 mg twice daily and 45 mg once daily, respectively. Baseline characteristics were similar between groups, with the exception of fasting C-peptide, which was statistically lower compared to pioglitazone in patients randomly assigned to *Avandia*. The primary endpoint was to assess the TG lowering effect of *Avandia* compared to pioglitazone. The effects of *Avandia* and pioglitazone on lipid parameters following 24 weeks of therapy are provided in Table 34.

Table 34. Effects of *Avandia* and Pioglitazone on Lipid Parameters at Week 24

Lipid Parameter	*Avandia*	Pioglitazone
Triglycerides (mg/dL)	n = 356	n = 363
Baseline	235.3 ± 6.6	257.8 ± 8.2
Change at Week 24	13.1 ± 7.8	-51.9 ± 7.8*†
% Change from baseline	14.9 ± 3.1*	-12.0 ± 3.0*†
Total Cholesterol (mg/dL)	n = 356	n = 363
Baseline	193.4 ± 1.8	193.6 ± 1.6
Change at Week 24	28.2 ± 1.9*	8.8 ± 1.9*†
% Change from baseline	15.9 ± 1.0*	5.7 ± 1.0*†
HDL-cholesterol (mg/dL)	n = 356	n = 363
Baseline	39.8 ± 0.6	38.8 ± 0.5
Change at Week 24	2.4 ± 0.5*	5.2 ± 0.5*†
% Change from baseline	7.8 ± 1.2 *	14.9 ± 1.2*†
LDL-cholesterol (mg/dL)	n = 356	n = 363
Baseline	109.1 ± 1.4	107.1 ± 1.3
Change at Week 24	21.3 ± 1.6*	12.3 ± 1.6*†
% Change from baseline	23.3 ± 1.9*	15.7 ± 1.9*‡
TC: HDL Ratio	n = 356	n = 363
Baseline	5.1 ± 0.1	5.3 ± 0.1
Change at Week 24	0.7 ± 0.1*	-0.3 ± 0.1*†
Apolipoprotein B (g/L)	n = 356	n = 363
Baseline	1.04 ± 0.01	1.05 ± 0.01
Change at Week 24	0.11 ± 0.01*	0.00 ± 0.01†

Data are means ± standard error. * $P \leq 0.05$ from baseline, change from baseline and percentage change from baseline are least-square means adjusted for baseline levels; † $P < 0.001$ vs. comparator; ‡ $P = 0.002$ vs. comparator.

HDL = high-density lipoprotein; LDL = low-density lipoprotein; TC = total cholesterol.

There were no observed differences between treatment groups with regard to body weight changes, liver function tests, creatine phosphokinase, blood pressure, heart rate, hemoglobin, hematocrit, hypoglycemic events, edema and congestive heart failure.

In a 12-month, randomized, double-blind study, the glycemic and lipid effects of *Avandia* or pioglitazone in combination with glimepiride were evaluated in 91 patients with type 2 diabetes and metabolic syndrome. [142] All patients had previously been diagnosed with metabolic syndrome according to the National Cholesterol Education Program Adult Treatment Panel III classification. Patients inadequately controlled or who experienced ≥ 1 adverse event with, diet and oral hypoglycemic agents given up to the maximum tolerated dose, received glimepiride 2 mg twice daily. In addition, patients were also randomized to receive *Avandia* 4 mg once or pioglitazone 15 mg once daily. There were no significant differences in the baseline characteristics between groups, and diet and exercise counseling was provided to all patients. The 12-month results are summarized in Table 35.

Table 35. Comparison of *Avandia* or Pioglitazone Plus Glimepiride at 12 Months [142]

Lipid Parameter	*Avandia* + glimepiride n = 42		Pioglitazone + glimepiride n = 45	
	Baseline	12 Months	Baseline	12 Months
Total Cholesterol, mg/dL	195 ± 24	224 ± 26*	190 ± 23	179 ± 18*†
LDL, mg/dL	121 ± 17	141 ± 20*	125 ± 15	110 ± 13*†
HDL, mg/dL	42 ± 5	43 ± 4	40 ± 4	46 ± 5*†
Triglycerides, mg/dL	162 ± 29	191 ± 32*	156 ± 35	121 ± 28*†
Apolipoprotein A-1	127 ±20	128 ±19	125 ±18	130 ±23
Apolipoprotein B	117 ±22	129 ±25*	113 ±21	101 ±18*†

Data are means ± SD. *$P < 0.05$ vs. baseline; † $P < 0.05$ vs. *Avandia* plus glimepiride.

There were no serious adverse events reported in either group and no study discontinuations as a result of an adverse event. [142] A total of 5 out of 42 (11.9%) patients treated with *Avandia* plus glimepiride and 3 out of 45 (6.7%) patients in the pioglitazone plus glimepiride group experienced mild to moderate adverse events. Overall, there were no statistically significant changes observed in mean aminotransferase activities from baseline to 12 months in either treatment group.

The efficacy and safety of *Avandia* was compared to pioglitazone and placebo in a 28 week, multicenter, randomized, placebo controlled, double-blind, parallel-group study involving 373 Japanese patients with type 2 diabetes (HbA1c ≥ 7.4%).(143) The primary endpoints were change in baseline HbA1c at week 28 for *Avandia* (4 mg and 8 mg combined) and pioglitazone (30 mg and 45 mg combined) as well as change in baseline HbA1c at week 16 with *Avandia* 4 mg, pioglitazone 30 mg and placebo, in type 2 diabetic patients inadequately controlled by diet alone. Subjects with hyperlipidemia (LDL ≥ 120 mg/dL or TC ≥ 200 mg/dL) within 3 months prior to baseline and not on HMG-CoA reductase inhibitors, were excluded from the study. Laboratory tests were performed at baseline, every 4 weeks until study end, or at withdrawal, and at post-treatment examination (week 30 or 2 weeks after withdrawal). The effects of *Avandia* and pioglitazone on lipid parameters are provided in Table 36.

Table 36. Comparison of Lipid Parameters at Week 28 for *Avandia* and Pioglitazone(143)

Lipid Parameter	*Avandia* (N = 159)	Pioglitazone (N = 159)	Placebo (N = 54)
Triglycerides (mg/dl)			
Mean baseline	157.6±150.03	148.0±115.79	148.4±107.94
Mean at week 28	142.5±128.41	119.6±101.63	149.9±113.34
% Change from baseline	-15.7±98.76	-30.9±110.14	-5.2±112.49
Total Cholesterol (mg/dl)			
Mean baseline	192.6±28.81	191.0±29.25	190.4±27.44
Mean at week 28	204.8±38.07	195.6±33.60	191.6±34.28
% Change from baseline	11.6±30.19	5.3±28.30	3.1±29.01
HDL-Cholesterol			
Mean baseline	55.4±13.48	54.5±13.14	55.9±12.75
Mean at week 28	59.5±14.91	62.5±15.58	55.9±12.75
% Change from baseline	4.2±8.80	8.1±8.86	2.1±7.05
LDL-Cholesterol			
Mean baseline	112.3±26.57	113.2±27.31	110.2±26.01
Mean at week 28	120.7±31.26	113.0±29.67	110.7±31.26
% Change from baseline	7.5±26.60	0.6±25.01	2.1±25.05
LDL Particle Size			
Mean baseline	0.359±0.0359	0.363±0.0323	0.362±0.0391
Mean at week 28	0.343±0.0405	0.336±0.0354	0.360±0.0391
% Change from baseline	-0.016±0.0379	-0.027±0.0314	-0.005±0.0293
Data are means ±SD HDL = high-density lipoprotein; LDL = low-density lipoprotein			

The most frequently reported adverse events in the rosiglitazone group were nasopharyngitis (20.8%) followed by edema (9.4%), diarrhea (5.0%), weight gain (4.4%), and upper respiratory tract inflammation (4.4%). The most frequently reported adverse events in the pioglitazone group were edema (22.6%) followed by nasopharyngitis (17.0%), weight gain (9.4%), upper respiratory tract inflammation (5.7%), increase in brain natriuretic peptide (5.0%), back pain (5.0%) and dizziness (5.0%).(143) Four subjects in the rosiglitazone group, 14 subjects in the pioglitazone group, and 1 subject in the placebo group withdrew from the study due to adverse events.

In a retrospective data analysis, *Avandia* (n = 99), pioglitazone (n = 98), and troglitazone (no longer marketed; n = 90), were evaluated in 287 patients with type 2 diabetes previously treated with a thiazolidedione (TZD) for ≥ 300 and ≤ 900 days.(12) The analysis was conducted to determine the long-term effects on glycemic control, lipid parameters, blood pressure, weight, edema, and liver function. There was no significant differences among treatment groups at baseline with a mean age of ~ 58.6 yrs and duration of diabetes ~ 10.8 years. Mean baseline A1c was slightly higher, although non-significant, in the pioglitazone group (8.98%) as compared to the *Avandia* (8.85%) and troglitazone (8.55%) groups. There were no significant differences with regard to lipid parameters at baseline (mean total cholesterol (TC) = 195.5 mg/dl; mean low-density lipoprotein (LDL) = 112..3 mg/dl; mean high-density lipoprotein (HDL) = 45.6 mg/dl; mean triglycerides (TG) = 262.5 mg/dl). Significant decreases were observed for TC, LDL, and TG upon initiation of a TZD in each treatment group. A statistically significant increase in HDL was reported in patients receiving *Avandia* or pioglitazone as compared to troglitazone. There were no statistically significant differences among the treatment groups with regard to TC, LDL, or TG. The most common subjectively reported adverse events included weight gain, edema, hypoglycemia, and dyspnea. There were no significant differences among adverse events between *Avandia*, pioglitazone, and troglitazone treatment groups.

An additional retrospective data analysis evaluated *Avandia* (n = 590) and pioglitazone (n = 525) in type 2 diabetes patients previously treated with a thiazolidinedione (TZD) for ≥ 12 weeks.[(144)] This analysis was conducted to evaluate the mean change in serum triglycerides (TG), total cholesterol (TC), high-density lipoprotein (HDL), low-density lipoprotein (LDL), and HbA1c between treatment groups. There were no significant differences with baseline demographics among treatment groups. Mean age was ~60 years with a body mass index (BMI) of ~ 33kg/m^2 and duration of TZD therapy of ~17 weeks. Additionally, there were no significant differences with regard to comorbidities and concomittant medications among treatment groups. A statistically significant reduction in mean change of TG was reported with pioglitazone (-55.17 mg/dl) as compared with *Avandia* (-13.34 mg/dl; $P < 0.001$). A reduction in mean change of TC was reported with pioglitazone (-8.45mg/dl) as compared with *Avandia* (4.81 mg/dl; $P < 0.001$). Additionally, a statistically significant reduction in LDL was reported with pioglitazone as compared with *Avandia* (-5.05 mg/dl vs. 3.56 mg/dl; $P < 0.001$). Mean change in serum HDL increased with pioglitazone (2.65 mg/dl) and decreased with *Avandia* (-0.12 mg/dl), although this was not statistically significant. Reduction in HbA1c were equivalent between the pioglitazone and *Avandia* treatment groups respectively (-1.04% vs -1.18%). Both pioglitazone and *Avandia* treatment groups had a significant increase from baseline in body weight of 1.97 lbs and 1.64 lbs respectively. ($P < 0.001$ vs. baseline).

8. OTHER STUDIED USES

8.1 Use of *Avandia* in the Prevention or Delay of Type 2 Diabetes with Impaired Glucose Tolerance and/or Impaired Fasting Glucose

Clinical Information

The Diabetes REduction Assessment with ramipril and rosiglitazone Medication (DREAM) trial was an international, multicenter, randomized, double-blind, 2 x 2 factorial designed study with a median follow-up of 3 years.[(145)] DREAM was conducted to determine if *Avandia* or ramipril could prevent diabetes or reduce the risk of developing type 2 diabetes in people with impaired glucose tolerance (IGT) and/or impaired fasting glucose (IFG), commonly known as pre-diabetes. Pre-diabetes is defined as a condition when blood sugar levels are elevated above the normal range, but not enough to meet the current clinical diagnosis of type 2 diabetes.[(146)] Pre-diabetes is a precursor to type 2 diabetes. However, not all people with pre-diabetes will progress to develop clinical disease.

A total of 24,592 participants were screened of which 5,269 were randomized to receive either *Avandia* (n=2635) or placebo (n=2634).[(65)] Eligible participants for the trial were those aged 30 or over with IGT or IFG and no diabetes [fasting plasma glucose (FPG) ≥110 mg/dl and < 126 mg/dl, and a 2-h plasma glucose < 200 mg/dl after a 75-gram oral glucose tolerance test (OGTT)].[(145)] Of those randomized, 3028 (57%) had isolated IGT, 739 (14%) had isolated IFG, and 1502 (29%) had both disorders.[(65)] The majority of patients were female (59.2%) with a mean age of 54.7 years and body mass index (BMI) of 31 kg/m^2. All patients received healthy eating and exercise counseling. Participants with a history of diabetes, cardiovascular disease, or intolerance/hypersensitivity to either angiotensin-converting enzyme inhibitors or thiazolidinediones were excluded from the study.

A run-in period of 17 days was followed by a 3-5 year treatment period with double-blind study medication. Participants were randomized to receive ramipril 5mg/day or placebo and *Avandia* 4mg/day or placebo using a 2X2 factorial design. During the treatment period, up-titration was required. Up-titration with *Avandia* from 4mg/day to 8mg/day occurred at 2 months. Up-titration with ramipril from 5mg/day to 10mg/day occurred at 2-months, and then up-titration to 15mg/day took place at 1 year.

With regards to the 2X2 factorial analysis, DREAM was designed to compare active treatment groups (*Avandia* or ramipril) to the placebo groups and was not designed to compare rosiglitazone-containing regimens to ramipril-containing regimens. Thus the main comparisons were subjects receiving rosiglitazone (with or without ramipril) to subjects receiving rosiglitazone placebo (with or without ramipril) and subjects receiving ramipril (with or without rosiglitazone) to subjects receiving ramipril placebo (with or without rosiglitazone).

The composite primary endpoint was the development of diabetes, or all-cause mortality, during the active treatment period. All-cause mortality was included to control for the chance that diabetes may develop at a rate that is different in subjects who die than in those who survive. Participants were assessed every 6 months following randomization for the duration of the study. Diagnosis of type 2 diabetes was defined as:

- Exceeding plasma glucose thresholds of FPG ≥126 mg/dl or 2 hr OGTT ≥ 200 mg/dl on any 2 consecutive occasions in a 3-month period
- Any single glucose concentration consistent with diabetes if a second confirmatory result could not be obtained
- Diagnosis by an outside physician with a confirmatory glucose concentration of either FPG ≥126 mg/dl or 2 hr OGTT ≥ 200 mg/dl and an oral hypoglycemic agent prescribed

In addition to determining whether treatment with *Avandia* or ramipril would prevent or reduce the risk of development of type 2 diabetes in participants with IGT and/or IFG, the following secondary endpoints were also evaluated: (1) regression to normal fasting and 2-hour post-load glucose concentrations (FPG < 110 mg/dl, 2-hr plasma glucose concentration < 140 mg/dl), (2) composite of cardiovascular (CV) events (myocardial infarction (MI), stroke, cardiovascular death, revascularization, heart failure, new angina with objective evidence of ischemia, or ventricular arrhythmia requiring resuscitation), (3) individual components of the cardiovasular composite, (4) renal events and a composite cardiorenal outcome, and (5) glucose concentrations.

A 3-month washout evaluation has been conducted to assess the durability of *Avandia* in reducing the risk of type 2 diabetes. The results of this analysis have not been published.

There was a 60% risk reduction in the composite primary endpoint of diabetes or death in participants receiving *Avandia* compared to placebo [11.6% vs. 26%; Hazard Ratio (HR) 0.40, 95% Confidence Interval (CI) 0.35-0.46; $P < 0.0001$].[65] A 62% risk reduction in the progression to type 2 diabetes was demonstrated in participants receiving *Avandia* compared to placebo [10.6% vs. 25%; HR 0.38, 95% CI 0.33-0.44; $P < 0.0001$]. There was a non-significant difference in the frequency of death between the *Avandia* and placebo groups (1.1% vs. 1.3%; $P = 0.7$). The effect of *Avandia* remained consistent regardless of age, sex, and geographic regions. Additionally, a greater reduction in the primary endpoint of diabetes or death was seen in the subgroup of participants with a body mass index (BMI) > 32 kg/m^2 (HR 0.32, 95% CI 0.25-0.40) compared to participants with a BMI < 28 kg/m^2 (HR 0.60, 95% CI 0.48-0.77; *P*-value for heterogeneity = 0.0004).

Fasting plasma glucose concentrations and 2-hr plasma glucose levels were significantly lower in the *Avandia* group compared to placebo ($P < 0.0001$). In the secondary outcome analysis, a significantly larger number of participants receiving *Avandia* achieved normoglycemia (FPG < 110 mg/dl and a 2-hr plasma glucose <140 mg/dl) compared to placebo (50.5% vs. 30.3%, $P < 0.0001$). Participants receiving *Avandia* were 71% more likely to regress to normoglycemia compared to placebo. [HR 1.71, 95% CI 1.57-1.87; $P < 0.0001$].

There was no statistically significant difference in the composite cardiovascular endpoint (2.9% for *Avandia* and 2.1% for placebo; $P = 0.08$). All but one of the individual components of the cardiovascular composite (MI, stroke, CV death, new angina and revascularization) also showed no statistically significant difference between the groups. There was a statistically significant higher incidence of reported heart failure in the *Avandia* group (n=14) compared to the placebo group (n=2) (0.5% vs 0.1%; $P = 0.01$). All cases of heart failure were non-fatal.

Mean systolic and diastolic blood pressures were significantly lower in the Avandia group compared to placebo (1.7 mmHg vs 1.4 mmHg; $P < 0.0001$). Mean body weight increased by 2.2 kg more with *Avandia* compared to placebo ($P < 0.0001$). This may have been the result of fat accumulation in non-visceral compartments and an increase in subcutaneous mass. Mean hepatic ALT concentrations were 4.2 U/L lower in the participants who received *Avandia* compared to placebo during the first year of therapy ($P < 0.0001$).

The most frequent reasons for withdrawal included the following: (1) Participant refusal (18.9% *Avandia* vs 16.7% placebo), (2) Edema (4.8% *Avandia* vs 1.6% placebo), (3) Physician's advice (1.9% *Avandia* vs. 1.5% placebo) and (4) Weight gain (1.9% *Avandia* vs 0.6% placebo). There was 1 discontinuation due to hypoglycemia with *Avandia* and 3 with placebo.

In preliminary analyses of the DREAM trial, the hazard ratios for the risk of major adverse cardiovascular events (MACE- myocardial infarction, cardiovascular death, or stroke), myocardial infarction, and total mortality with *Avandia* compared with a control group were calculated and are presented in Table 37.[147]

Table 37. Hazard Ratios for the Risk of MACE, Myocardial Infarction, and Total Mortality[147]

	MACE		Myocardial Infarction		Total Mortality	
	n (%)	HR (95% CI)	n (%)	HR (95% CI)	n (%)	HR (95% CI)
RSG N = 1325	15 (1.1)		5 (0.4)		15 (1.1)	
vs placebo N = 1321	14 (1.1)	1.07 (0.51, 2.21)	7 (0.5)	0.71 (0.23, 2.24)	17 (1.3)	0.87 (0.44, 1.75)
RSG + RAM N = 1310	18 (1.4)		12 (0.9)		15 (1.1)	
vs RAM N = 1313	9 (0.7)	2.01 (0.90, 4.48)	5 (0.4)	2.41 (0.85, 6.84)	16 (1.2)	0.94 (0.47,1.90)

MACE = major adverse cardiovascular events; HR = hazard ratio; CI = confidence interval; RSG = rosiglitazone; RAM = ramapril

In a prospective, randomized trial, Durbin evaluated the early use of thiazolidinediones (TZDs) on the prevention or delay of type 2 diabetes in multi-ethnic patients with impaired glucose tolerance (IGT) and insulin resistance (defined as normal or borderline HbA1c, C-peptide level > 2 mg/ml, fasting plasma glucose (FPG) between 100 and 125 mg/dL, and 2-hour postprandial blood glucose between 140 and 200 mg/dL) for a mean duration of 36 months. [148] A total of 172 patients aged 29-86 years were randomized to receive *Avandia* 4 mg once daily or pioglitazone 30 mg/day with possible titration. Patients in the active treatment group (n = 101) received troglitazone for an average of 10 months before being randomized to *Avandia* or pioglitazone. Patients in the control group (n = 71) were not taking any antidiabetic medication during the study. Antihypertensive and lipid-lowering agents were prescribed as necessary; however no patients received other oral antidiabetic medications or insulin. Results of this study are presented in Table 38.

Table 38. Effect of *Avandia* and Pioglitazone in on HbA1c and C-peptide in Patients with IGT and Insulin Resistance* [148]

	Avandia	**Pioglitazone**	**Control**
HbA1c (%)†			
Baseline	6.12	6.23	6.18
HbA1c at time of switch from troglitazone	5.69‡	5.79‡	6.25§
2-year follow-up	5.61‡	5.64‡	6.53§
Final	5.57‡	5.65‡	6.68§
C-peptide (mg/ml)†			
Baseline	3.39	3.9	3.56
Final	1.69	1.84	4.46
Total patients developing type 2 diabetes at study end	1	2	19

* Includes 101 patients treated with *Avandia* or pioglitazone and 71 patients in the control group.

† Mean value presented for each evaluation time point; ‡ $P < 0.05$ vs. baseline; § $P < 0.01$ vs. *Avandia* and pioglitazone

As shown in the above table, mean HbA1c levels were reduced in patients receiving TZD treatment at 2 years and were maintained at study endpoint. [148] Progression to type 2 diabetes was also reduced in patients receiving TZD treatment compared to control at study endpoint.

A systematic collection of adverse events was not performed. However, an increase in weight was noted from baseline of 5.4 lbs per patient in the pioglitazone group, and 0.7 lbs per patient in the *Avandia* group. [148] A few patients in the treatment group also experienced fluid retention, but causality with treatment was not established. The authors suggest that TZDs are effective in reducing HbA1c and C-peptide levels in patients with IGT and insulin resistance, and may be beneficial in helping to prevent type 2 diabetes. Long-term outcome studies are needed to confirm these preliminary findings.

A randomized, double-blind, placebo-controlled study was conducted in Europe to determine the effect of *Avandia* on insulin sensitivity in patients with IGT. [149,150] Whole body insulin sensitivity was measured by deriving an insulin sensitivity index (ISI) from a euglycemic hyperinsulinemic clamp. Following a 4-week, single-blind, placebo run-in period, 18 subjects with persistent IGT were randomized to receive either *Avandia* 4 mg twice daily or placebo for 12 weeks. IGT was defined as a 2-hour oral glucose tolerance test (OGTT) of ≥ 7.8 mmol/L and < 11.1 mmol/L and a FPG of < 7.8 mmol/L. The primary efficacy parameter was the mean change in ISI at study endpoint compared to baseline.[150]

The intent-to-treat population consisted of 18 subjects equally distributed between the two groups.[150] Overall, subjects participating in the trial were Caucasian with 56% of the subjects being male. The mean age was 59.8 years. The mean body mass index was slightly greater for subjects receiving *Avandia* (30.2 kg/m^2) than in the placebo group (28.8 kg/m^2).

The results of *Avandia* on insulin sensitivity index (ISI; primary efficacy parameter) and 24-hour ambulatory blood pressure (ABP) from this study were reported. [149] Following 12 weeks of treatment, *Avandia* improved ISI by 2.26 ug/kg/min/pmol/L compared to placebo ($P = 0.0003$). [149,150] ISI increased from a baseline value of 7.09 to 8.81 ug/kg/min/pmol/L in subjects receiving *Avandia* and decreased from a baseline of 9.94 to 8.12 ug/kg/min/pmol/L in the placebo group. A statistically significant reduction in mean 24-hour systolic and diastolic blood pressure was observed in subjects receiving *Avandia* compared to placebo and baseline. Overall, there was little change in FPG and HbA1c following 12 weeks of therapy with *Avandia* or placebo. Additionally, no significant treatment differences in insulin, proinsulin, and C-peptide concentrations were observed in either group.[150]

Avandia significantly decreased glucose AUC(0-3 hr) following both an OGTT ($P = 0.0464$) and a mixed meal tolerance test (MMTT) ($P = 0.0176$) compared to placebo. [149] Of the 9 patients treated with *Avandia*, four developed normal glucose tolerance and 5 continued to exhibit IGT, although four of these patients had improved 2-hour glucose values. In the placebo group, 1 subject out of 9 progressed to type 2 diabetes and 8 out of 9 retained IGT.

Adverse events reported in more than one subject following treatment with *Avandia* were abdominal pain, vomiting, anemia, upper respiratory tract infections, dyspnea, epistaxis and leg cramps (all reported in 2 out of 9 subjects).[150] In the placebo group, commonly reported adverse events included dizziness and increased gamma-glutamine transferase (GGT) (both reported in 2 out of 9 subjects). No reports of hypoglycemia were noted in either group. No subjects were withdrawn during the study due to an adverse experience.

8.2 Coadministration of *Avandia* with Insulin for the Treatment of Type 2 Diabetes

The U.S. Food and Drug Administration conducted a retrospective meta-analysis to assess the cardiovascular adverse events of *Avandia* added to insulin across five, 26 week, randomized, controlled, double-blind, trials.[64] In studies where *Avandia* was added to insulin, *Avandia* increased the risk of congestive heart failure and myocardial ischemia (See Table 39). Patients with type 2 diabetes mellitus were randomized to coadministration of *Avandia* and insulin (N = 867) or insulin (N = 663). These trials included patients with history of diabetes (median duration of 12 years), peripheral neuropathy, retinopathy, ischemic heart disease, vascular disease, and congestive heart failure. The total number of patients with emergent congestive heart failure was 21 (2.4%) in the *Avandia* and insulin group and 7 (1.1%) in the insulin group. The total number of patients with emergent myocardial ischemia was 24 (2.8%) and 9 (1.4%) in the *Avandia* plus insulin and insulin groups, respectively (Odds Ratio (OR) 2.1 [95% Confidence Interval (CI) 0.9, 5.1]). Although the event rate for congestive heart failure and myocardial ischemia was low in the studied population, consistently the event rate was 2-fold or higher with coadministration of *Avandia* and insulin. These cardiovascular events were noted at both the 4 mg and 8 mg daily doses of *Avandia*.

Table 39. Occurrence of Cardiovascular Events in 5 Controlled Trials of Addition of *Avandia* to Established Insulin Treatment [64]

* Event	*Avandia* + Insulin (n = 867) n (%)	Insulin (n = 663) n (%)
Congestive heart failure	21 (2.4%)	7 (1.1%)
Myocardial ischemia	24 (2.8%)	9 (1.4%)
Composite of cardiovascular death, myocardial infarction, or stroke	10 (1.2%)	5 (0.8%)
Stroke	5 (0.6%)	4 (0.6%)
Myocardial infarction	4 (0.5%)	1 (0.2%)
Cardiovascular death	4 (0.5%)	1 (0.2%)
All deaths	6 (0.7%)	1 (0.2%)

* Events are not exclusive; i.e., patient with a cardiovascular death due to a myocardial infarction would be counted in 4 event categories (myocardial ischemia; cardiovascular death, myocardial infarction or stroke; myocardial infarction; cardiovascular death)

GSK Integrated Clinical Trials Analysis

As part of its ongoing monitoring and assessment of the safety of *Avandia*, GlaxoSmithKline (GSK) proactively conducted a series of retrospective analyses to characterize the degree of association, if any, between *Avandia* and events including congestive heart failure (CHF) and myocardial ischemia.[11] Forty-two controlled and blinded clinical trials (mean duration 6 months) that included 4 mg or 8 mg doses of *Avandia* were included in this integrated clinical trials (ICT) analysis. Observations regarding CHF and *Avandia* therapy remain consistent with reports and observations from individual and integrated controlled clinical trials of an increased incidence of CHF in patients treated with *Avandia* and insulin combinations.

Additionally, in the ICT analysis, an increased risk of myocardial ischemic events was observed in the subset of patients with *Avandia* added to insulin therapy (24 patients with an event out of 867 patients) compared with placebo added to insulin therapy (9 patients with an event out of 663 patients); (Hazard Ratio (HR) 2.06, [95% CI: 0.96, 4.44]).

Clinical Trial Information

The clinical trial program for the use of *Avandia* in combination with insulin consisted of four double-blind trials of 26-week duration (Studies 082, 095, 136, 085). The two pivotal trials, studies 082 and 095, were fixed-dose in design and are discussed in detail below. [63,90,91,151,152]. Study 136 evaluated type 2 diabetes patients with chronic renal failure (112 patients received *Avandia* 4 mg or 8 mg plus insulin and 108 patients received insulin control)[63]. Study 085 evaluated the effect of *Avandia* (forced titration from 4 mg to 8 mg) on insulin requirements in well-controlled insulin-treated patients.[152]

The efficacy and safety of *Avandia* in combination with insulin were evaluated in two randomized, 26-week, fixed-dose, double-blind, placebo-controlled trials. [90,91,151] Following a 4-week, placebo run-in period, patients inadequately controlled (fasting plasma glucose (FPG) ≥ 140 mg/dL) on twice daily insulin injections were randomized to receive *Avandia* 4 mg/day, *Avandia* 8 mg/day, or placebo in addition to insulin.[90,91] Once randomized, the dose of insulin remained fixed. Insulin dose reductions were permitted only in response to sustained hypoglycemia (mean capillary glucose ≤ 100 mg/dL for 7 days) or severe or recurrent episodes of hypoglycemia. The primary efficacy parameters in both studies were the mean change from baseline and placebo in HbA1c at the end of 26 weeks of therapy. Treatment with *Avandia* 4 mg or 8 mg/day in combination with insulin significantly reduced HbA1c and FPG compared to both baseline values and insulin alone in both studies. Adverse events occurred in ≥ 5% of patients in any treatment group are presented in Table 40.[90] [91,153] In general, the majority of adverse experiences were considered mild to moderate in intensity and unrelated to the study medication. Overall, 6.8% of patients receiving *Avandia* 4 mg/day plus insulin and 8.9% of patients receiving *Avandia* 8 mg/day plus insulin, respectively withdrew from therapy due to an adverse event.

Table 40. Adverse Events Reported in ≥ 5% of Patients During Pre-approval Pivotal Clinical Studies[90,91,153]

	***Avandia* 4 mg/day + Insulin**	***Avandia* 8 mg/day‡ + Insulin**	**PBO + Insulin**
	n = 206	n = 202	n = 203
Preferred Term	%	%	%
Hypoglycemia*	57.3	68.8	41.4
Upper respiratory tract infection	22.3	20.8	20.2
Anemia	7.3	14.4	3.4
Infection viral	7.8	9.9	7.9
Injury†	8.3	9.9	9.4
Urinary Tract Infection	3.9	8.4	9.9
Edema dependent	3.9	7.9	1.5
Hyperlipemia	2.4	7.4	3
Weight Increase	3.4	5.9	1.5
Coughing	2.4	5.4	3.0
Edema legs	4.9	5.4	2.5
Headache	4.9	5.4	7.4
Sinusitis	6.8	5.4	7.9
Bronchitis	5.3	4.5	3.4
Pain	4.4	4.5	5.4
Arthralgia	6.3	3.5	3.4
Diarrhea	2.4	3.5	6.9
Hypertension Aggravated	3.4	2.5	5.9

*Defined by one of the following three criteria: suggestive signs and/or symptoms only (considered by the investigator to be an adverse experience); plasma or capillary blood glucose concentration of < 50 mg/dL; signs and/or symptoms requiring corrective therapy; †Injury includes items such as cuts, burns, sprains, fractures, accidents, and surgical procedures.

Safety and Efficacy of Low-dose *Avandia* added to Insulin

A 24-week, double-blind study evaluated the safety and efficacy of low-dose *Avandia* (2 or 4mg/day) added to insulin therapy compared with placebo added to insulin therapy in 630 patients with long-standing type 2 diabetes inadequately controlled on insulin therapy alone. [154] Patients were randomized to treatment with *Avandia* (2 or 4 mg/day) or placebo in combination with concurrent insulin therapy. The primary efficacy endpoint was change in HbA1c from baseline to week 24. All cardiovascular adverse events with potential relationship to fluid retention, or ischemia, including CHF, cardiac failure, pulmonary edema, cardiac arrest, myocardial infarction, myocardial ischemia, and sudden death were reviewed by an independent adjudication committee. The addition of *Avandia* (2 or 4 mg/day) to concurrent insulin therapy reduced HbA1c by -0.6% or -0.8%, respectively, from baseline ($P < 0.001$ for both) and by -0.3% ($P = 0.02$) and -0.4% ($P < 0.001$) compared to placebo. Significantly more patients achieved HbA1c < 7% in both *Avandia* 2 or 4 mg/day treatment groups compared to the placebo group. (13%, 14.4%, and 6.5%, respectively). The most frequently reported severe adverse event in all treatment groups was hypoglyemia. (154) Independently adjudicated cardiovascular events were low and similar among treatment groups. Reports of cardiovascular events were adjudicated to have occurred in 2.4%, 1.4% and 0.9% of patients treated with *Avandia* 2mg, *Avandia* 4 mg , and placebo, respectively. Most edema was reported as mild to moderate in intensity and was reported in 5.7%, 11% and 10.8% of patients receiving *Avandia* 2mg/day, *Avandia* 4mg/day and placebo, respectively. Two patients (1%) receiving *Avandia* 2 mg/day plus insulin and 2 patients (1%) receiving *Avandia* 4 mg/day plus insulin reported on-therapy adverse events of CHF. Additionally, 2 patients receiving *Avandia* 2 mg/day plus insulin reported serious on-therapy adverse events of myocardial infarction of which 1 was considered by the investigator to be related or potentially related to study medication. (155) Significant weight gain occurred in all 3 treatment groups. (154) A dose-related increase in mean weight was observed from baseline to week 24 in patients treated with *Avandia* 2mg/day and *Avandia* 4 mg/day plus insulin (1.94 kg and 3.16 kg, respectively). Mean weight gain over 24 weeks was lowest in the placebo group plus insulin group (0.84 kg).

8.3 Use of *Avandia* in Type 2 Diabetes Patients with Heart Failure

Avandia vs. Placebo in Type 2 Diabetes Patients with NYHA Class I or II CHF

A 52-week, double-blind, placebo-controlled, non-inferiority echocardiographic study was conducted in 224 patients with type 2 diabetes and NYHA Class I or II CHF.(68) Patients with an ejection fraction ≤ 45% treated with angiotensin converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs) and/or diuretics at study entry were randomized to *Avandia* (4 mg/day increased to 8 mg/day) or placebo in addition to background antidiabetic therapy. Background antidiabetic therapy included diet, exercise and/or oral monotherapy or oral combination therapy of no more than 2 medications (insulin therapy was excluded at entry to the study and was not permitted during the study except during acute episodes such as hospitalization, trauma, or infection to manage glycemic control). (68)The dose and regimen of oral antidiabetic therapy could be changed to achieve glycemic control. However, initiation or uptitration of metformin was not permitted during the study due to the risk of lactic acidosis. If a patient experienced signs or symptoms of fluid-retention or an exacerbation of CHF, CHF medications could be adjusted by optimizing diuretic therapies, adjusting background ACEI/ARB therapy, adding cardiac glycosides, or the dose of *Avandia* could be reduced.

An independent committee conducted a blinded evaluation of fluid-related events (including CHF) and cardiovascular hospitalizations according to predefined criteria (adjudication).(68) Separate from the adjudication, other cardiovascular adverse events were reported by investigators. Although no treatment difference in change from baseline of ejection fractions was observed, more cardiovascular adverse events were observed with *Avandia* compared to placebo during the 52-week study (Table 8Table 41).

Table 8. Emergent Cardiovascular Adverse Events (Study 211)(68)Table 41. Emergent Cardiovascular Adverse Events (Study 211)(68)

	Avandia	**Placebo**	**P-value**
EVENTS	N = 110 n (%)	N = 114 n (%)	
Major Adjudicated Clinical Endpoints			
Cardiovascular Death	5 (4.8)	4 (3.8)	0.85
All-cause Mortality	8 (7.7)	5 (4.8)	0.48
All-cause Mortality or Worsening CHF	11 (10.6)	8 (7.5)	0.59
Other Adjudicated Clinical Endpoints			
Cardiovascular Hospitalization*	21 (19.1)	15 (13.2)	0.47
Definite Worsening CHF	5 (4.5)	4 (3.5)	0.86
Possible Worsening CHF	2 (1.8)	0	N/A †
New or Worsening Edema	28 (25.5)	10 (8.8)	0.01
New or Worsening Dyspnea	29 (26.4)	19 (16.7)	0.20

	Avandia	Placebo	P-value
Increase in CHF Medication	36 (32.7)	20 (17.5)	0.04
* Major reasons for cardiovascular hospitalization included worsening of CHF, myocardial infarction, and stroke/transient ischemic attack † No events occurred in one treatment group, preventing analysis using this model			

Avandia, like other thiazolidinediones, alone or in combination with other antidiabetic agents, can cause fluid retention, which may exacerbate or lead to heart failure.(7) Coadministration of *Avandia* and insulin is not recommended. In studies where *Avandia* was added to insulin, *Avandia* increased the risk of congestive heart failure and myocardial ischemia. Patients should be observed for signs and symptoms of heart failure. If these signs and symptoms develop, the heart failure should be managed according to current standards of care. Furthermore, discontinuation or dose reduction of rosiglitazone must be considered. *Avandia* is not recommended in patients with symptomatic heart failure. Initiation of *Avandia* in patients with established NYHA Class III or IV heart failure is contraindicated.

8.4 *Avandia* and Polycystic Ovary Syndrome (PCOS)

Background

Polycystic Ovary Syndrome (PCOS) is an endocrinologic disorder of premenopausal women characterized by hyperandrogenism and chronic anovulation. (156) PCOS affects 5-10% of women of childbearing age and is the most common cause of female infertility in the United States. (157) (158) The most common presenting complaints of women with PCOS are menstrual irregularity and hirsutism. PCOS is associated with significant insulin resistance and with defects in insulin secretion. The insulin-like growth factor (IGF) axis is involved in the pathogenesis of hyperandrogenism. (159) IGF-1 is important in the regulation of ovarian follicular maturation and steroidogenesis and is increased in patients with adrenal hyperandrogenism. The insulin-like growth factor binding protein-1 (IGFBP-1) regulates IGF-1 bioavailability in tissues. (160) The insulin-like growth factor binding protein-3 (IGFBP-3) binds most circulating IGF-1 and decreased levels of IGFBP-3 appear to be an endocrinologic feature of PCOS. Strategies for the treatment of infertility associated with PCOS have included medications such as clomiphene citrate, metformin, and thiazolidinediones (TZDs). (158) (161)

Clinical Information

A double-blind, placebo-controlled study was conducted to assess the effects of *Avandia* on clinical symptoms, insulin and glucose metabolism, and hormonal parameters in 30 overweight women with PCOS [body mass index (BMI) >25 kg/m^2, mean age 29.1 ± 1.2 years, range 18-41].(162) All subjects included in the study had polycystic ovaries in vaginal ultrasonography and one or more of the following symptoms: oligomenorrhea, amenorrhea, clinical manifestations of hyperandrogenism, such as a hirsutism score of more than 7 and/or an elevated serum testosterone level (>2.7 nmol/l). Subjects were assigned to receive either placebo or *Avandia* 4 mg daily for 2 weeks followed by 4 mg twice daily for 4 months. Pregnancy was contraindicated during the study, and all subjects were advised to use some form of non-hormonal contraception. The two groups were comparable with regard to baseline characteristics with the exception of serum fasting C-peptide levels, serum testosterone levels, and serum dehydroepiandrosterone sulphate (DHEA-S) concentrations (see Table 42).

Two women became pregnant during treatment with *Avandia*, and the drug was stopped when they learned they were pregnant. A healthy child was delivered by one of the women, and the other had missed abortion at 10 gestational weeks and terminated the pregnancy by evacuation and abrasion. One woman in each group stopped the study for personal reasons and 2 in the *Avandia* group did not want to undergo the clamp test at 4 months. There were no drug-related adverse events reported. The clinical, metabolic, and hormonal parameters before and during treatment are shown in Table 42.

Table 42. Clinical, Metabolic, and Hormonal Parameters Before and During Treatment(162)

	Avandia		Placebo	
	Before (n = 12)	4 months (n = 12)	Before (n = 14)	4 months (n = 14)
Clinical Parameters				
Body mass index (kg/m^2)	33.1 ± 1.7	34.1 ± 1.8*	33.6 ±1.0	34.1 ± 1.2

	Avandia		Placebo	
	Before (n = 12)	4 months (n = 12)	Before (n = 14)	4 months (n = 14)
Waist-to-hip ratio	0.87 ± 0.12	0.80 ± 0.06	0.88 ± 0.01	0.88 ± 0.02
Hirsutism	8.92 + 0.9	8.45 + 0.9	9.86 + 1.5	10.29 + 1.6
Menstrual cycle length (days)	125 ± 35.9	39 ± 7.5†‡	93 ± 24.4	65 ± 10.2†
Metabolic Parameters				
Fasting blood glucose (mmol/l)	5.4 ± 0.2	5.2 ± 0.1†	5.4 ± 0.1	5.5 ± 0.1†
Fasting insulin (pmol/l)	12.4 ± 1.9	12.9 ± 3.0	15.0 ± 2.6	17.2 ± 2.7
Fasting C-peptide (nmol/l)	0.4 ± 0.06†	0.3 ± 0.08*	0.2 ± 0.04†	0.3 ± 0.05*
First-phase insulin secretion (pmol/mmol)	8.6 ± 1.16	10.3 ± 1.65	7.6 ± 1.85	8.1 ± 2.30
Fasting glucose oxidation (µmol/kg/min)	10.5 ± 1.06	9.33 ± 0.88	9.85 ± 1.12	9.5 ± 1.02
Fasting Free fatty acids (mmol/l)	0.53 ± 0.06	0.45 ± 0.04*	0.51 ± 0.45	0.53 ± 0.06
Fasting Lipid oxidation (mg/kg/min)	2.7 ± 0.45	2.9 ± 0.41	3.2 ± 0.41	3.4 ± 0.39
Clamp Free fatty acids (mmol/l)	0.06 ± 0.01	0.06 ± 0.02	0.07 ± 0.02	0.15 ± 0.07
Clamp Lipid oxidation (mg/kg/min)	2.0 ± 0.41	0.7 ± 0.28†	2.6 ± 0.31	2.4 ± 0.35†
Hormonal Parameters				
Testosterone (nmol/l)	2.7 ± 0.1†	2.7 ± 0.2	3.5 ± 0.3†	3.2 ± 0.3
Sex hormone-binding globulin (nmol/l)	30.3 ± 3.4	36.9 ± 5.2*	38.6 ± 5.3	36.2 ± 4.6
Free androgen index	10.3 ± 1.4	9.2 ± 1.6	11.4 ± 1.6	12.2 ± 2.5
Insulin-like growth factor-binding protein-1 (µg/l)	2.5 ± 0.5	3.3 ± 0.6	2.1 ± 0.3	2.2 ± 0.3
Androstenedione (nmol/l)	16.6 + 1.8	13.9 + 1.8*	16.3 + 1.7	16.8 + 1.5
Dehydroepiandrosterone (nmol/l)	58.2 ± 10.7	46.5 ± 9.0*	42.3 ± 5.7	46.2 ± 7.4
Dehydroepiandrosterone sulphate (µmol/l)	8.18 ± 0.9†	7.4 ± 1.3*	5.2 ± 0.7†	5.4 ± 0.8
17-Hydroxyprogesterone (nmol/l)	5.9 + 1.1	5.06 + 1.0*	4.7 ± 0.6	4.8 ± 0.6
Luteinizing hormone (IU/l)	6.4 ± 0.8	6.2 ± 1.2	6.9 ± 0.9	7.3 ± 0.9
Follicle stimulating hormone (IU/l)	4.8 ± 0.4	4.9 ± 0.4	4.9 ± 0.4	5.2 ± 0.4

Data are shown as mean ± SE. Results for clamp and calorimetry are given for n = 10 in the *Avandia* group and n = 14 in the placebo group. * $P < 0.05$ compared with the level before treatment. † $P < 0.05$ between *Avandia* and placebo groups. ‡ $P < 0.01$ compared with the level before treatment.

Shobokshi et al conducted a 12-week randomized, double-blind study to evaluate the effect of *Avandia* plus clomiphene citrate compared to clomiphene citrate monotherapy on the clinical and metabolic components of polycystic ovary syndrome (PCOS). [159] Fifty women with PCOS, diagnosis based on hyperandrogenism (plasma free testosterone > 6 pg/mL) and oligomenorrhea (< 6 menstrual periods in the previous 12 months or amenorrhea), were randomized to *Avandia* 4 mg/day for 12 weeks plus clomiphene citrate 100 mg on cycle days 5-9 (n = 25) or clomiphene citrate 100 mg on cycle days 5-9 (n = 25). No significant differences in baseline characteristics were noted between the two groups. Serum luteinizing hormone (LH) (> 12 mIU/mL), free testosterone (> 6 pg/mL), LH:follicle stimulating hormone (FSH) ratio (> 2), and area under the insulin curve (AUC insulin) were increased at baseline in all patients. Also, all women had normal serum prolactin levels, dehydroepiandrosterone sulfate (DHEAS) levels, and normal thyroid function. After treatment with *Avandia* and clomiphene citrate, improvement in menstrual pattern was noted in 92% (23/25) of the women compared to 68% (17/25) in the clomiphene citrate monotherapy group [odds ratio 0.185, 95% Confidence Interval (CI): 0.035, 0.993]. More specifically, regular menstrual cycles occurred in 72% (18/25) of the women treated with *Avandia* and clomiphene citrate compared to 48% (12/25) treated with clomiphene citrate monotherapy. Further results are presented in Table 1. Safety data were not presented for this study.

Table 43. Mean Hormonal, IGF-1, and IGFBP-3 Levels at Baseline and After Treatment [159]

	Avandia + clomiphene citrate		Clomiphene citrate monotherapy	
	n =25		n = 25	
	Baseline	After Treatment	Baseline	After Treatment
Serum LH (mIU/mL)	19.5	12.4*	18.8	16.2*
Serum FSH (mIU/mL)	4.98	7.16*	4.99	8.02*
Serum LH:FSH ratio	3.99	2.02*	4.05	2.06*
Serum estradiol (pg/mL)	52	58	49	52
Serum DHEAS (µg/dL)	199	187	210	186
Serum free testosterone (pg/mL)	8.94	4.62*	9.48	5.22*
Serum IGF-1 (ng/mL)	260	270	275	268
IGFBP-3 (ng/ml))	2424	3230*	2018	2982*
IGF-1:IGFBP-3 ratio	0.102	0.08*	0.13	0.110*
AUC insulin (µU/mL per minute)	8210	4800*	7840	7200

*$P < 0.05$ vs baseline

LH = luteinizing hormone, FSH = follicle stimulating hormone, DHEAS = dehydroepiandrosterone sulfate, IGF-1 = insulin-like growth factor 1, IGFBP-3 = insulin-like growth factor binding protein 3, AUC = area under the curve

Ghazeeri et al conducted a 2-month randomized, double-blind, placebo-controlled study to evaluate the effect of *Avandia* on ovulation induction in overweight and obese, clomiphene citrate resistant women with PCOS. [163] Patients were randomized to treatment with *Avandia* 4 mg twice daily with placebo on cycle days 5-9 (Group I, n = 12) or *Avandia* 4 mg twice daily with clomiphene citrate on cycle days 5-9 (Group II, n = 13). The primary outcome measure was ovulation measured by luteal serum progesterone (P4) > 5 ng/mL on days 21, 24, and 28 of the cycle. Secondary outcome measures included pregnancy and changes in insulin sensitivity, serum lipoproteins, and androgens. Overall, 56% (14/25) of the women who were previously resistant to clomiphene citrate successfully ovulated. In Group I, 33% (4/12) of the women ovulated compared with 77% (10/13) of the women randomized to Group II ($P = 0.04$). One patient in Group I became pregnant resulting in one uncomplicated live birth and two patients in Group II became pregnant with one successful live birth and one first trimester, spontaneous abortion. Excluding nonovulatory cycles, patients in Group II had a mean P4 value of 19.2 ng/mL compared with 10.2 ng/mL for Group I ($P = 0.05$). For all subjects, a significant decrease in mean fasting insulin levels was noted. Mean levels of total testosterone and DHEAS did not decrease significantly, but sex hormone-binding globulin (SHBG) increased significantly after therapy with *Avandia*. In addition, a significant decrease in mean luteinizing hormone (LH) levels was noted. Total cholesterol, low-density lipoprotein (LDL), high-density lipoprotein (HDL), and triglycerides did not change. A significant change in hematocrit was observed (40.3% [baseline] to 38.0% [$P = 0.008$]). One patient reported swollen fingers and another reported mild headaches, neither of which required withdrawal from the study.

A randomized, open-label study was conducted to examine the effects of metformin and *Avandia*, alone and in combination, on ovarian steroid production and excretion and on endometrial histology in women aged 18-40 years old with PCOS.[164] PCOS was defined in this study as an elevation of circulating androgen levels, either total testosterone > 58 ng/dL or free and weakly bound testosterone levels > 16 ng/dL, associated with chronic oligomenorrhea (≤ 6 menses per year) or amenorrhea. The study was 30 weeks in duration with a 6-week medication-free observation period followed by 12 weeks of single-agent therapy with metformin (1000 mg twice daily) or *Avandia* (4 mg twice daily) which was subsequently followed by 12 weeks of combined therapy with both agents. Participants were instructed to avoid pregnancy during the study by using barrier contraception. The baseline characteristics of the 2 groups were comparable except the metformin group tended to be heavier and the *Avandia* group had greater hyperinsulinemia during the oral glucose tolerance test. Compared to baseline, metformin had no significant effect on the sex steroid or glycemic measures. After 3 months of single-agent treatment, *Avandia* (n = 9) showed a benefit over metformin (n = 6) in decreasing free and weakly bound testosterone [-11.8 (95% CI: -21.7, -2.0 ng/dL); $P = 0.02$] and 2-hour insulin [-150.4 (95% CI: -272.7, -28.1 µU/mL); $P = 0.02$] and 2-hour glucose [-42.0 (95% CI: -76.2, -7.8 mg/dL); *P* = 0.02] obtained from oral glucose tolerance testing. The AUC insulin [-12,336 (95% CI: -22,001, -2671 (μU min)/mL); *P* = 0.02] and the insulin sensitivity index, 0 and 120 minutes [26.3 (95% CI: 6.6, 45.9); *P* = 0.01] were also significantly improved with *Avandia* compared to metformin. The *Avandia* group had a higher daily AUC pregnanediol-3-glucuronide (PdG)/estrone-1-glucuronide (E1G) compared to the metformin group (*P* = 0.01), but there were no differences in daily AUC E1G or PdG levels. The majority of measures were unaffected by combined therapy compared to single-agent therapy. However, at 6 months the addition of *Avandia* to metformin resulted in a significant weight gain in the metformin group. Although not statistically significant, the ovulation rate improved on single-agent therapy with metformin or *Avandia* compared to baseline. Five subjects did not ovulate during the 6 months of treatment alone or in combination. Endometrial histology tended to normalize during the study.

A 3 month prospective, open study, including 30 women 19-30 years of age (mean 24.3 ± 2.5) with PCOS and signs of insulin resistance, compared the clinical, biochemical, and hormonal changes associated with metformin or *Avandia* treatment.(165) The following parameters were studied at baseline and at 3 months: body mass index, waist-to-hip ratio, total testosterone, immune reactive insulin, sex hormone-binding globulin, dehydroepiandrosterone sulfate, free androgen index, homeostasis model of insulin resistance, triglycerides, total cholesterol, and high-density lipoprotein cholesterol. Patients received either metformin 850 mg twice daily with meals (n = 15) or *Avandia* 4 mg daily (n = 15). Patients in the *Avandia* group were advised to use barrier contraceptives during the study. At the end of the study, 2 parameters, testosterone and insulin levels, changed significantly. Compared to baseline, the mean difference in testosterone levels at month 3 was -0.65 (95% CI: -1.13, -0.17; *P* = 0.0094) in the metformin group but was not significant in the *Avandia* group [-0.48 (95% CI: -1.29, 0.33)]. The mean difference in insulin levels from baseline to month 3 was -3.50 (95% CI: -6.54, -0.46; *P* = 0.0257) in the metformin group and -3.70 (95% CI: -5.81, -1.59; *P* = 0.0012) in the *Avandia* group. Prior to treatment, 11 women in the metformin group and 12 in the *Avandia* group had oligo-amenorrhoea. Following therapy, 8 women in the metformin group and 10 in the *Avandia* group had regular menses. No serious adverse events were reported during the study. Five women (33%) in the metformin group and 3 (20%) in the *Avandia* group reported dyspeptic symptoms at the end of the first month which went away spontaneously. None of the patients stopped treatment early.

Additional studies using alternative combinations or dosing regimens have also shown *Avandia* to be beneficial in the treatment of women with PCOS.(166,167)

8.5 Rosiglitazone and Cognitive Impairment in Patients with Alzheimer's Disease

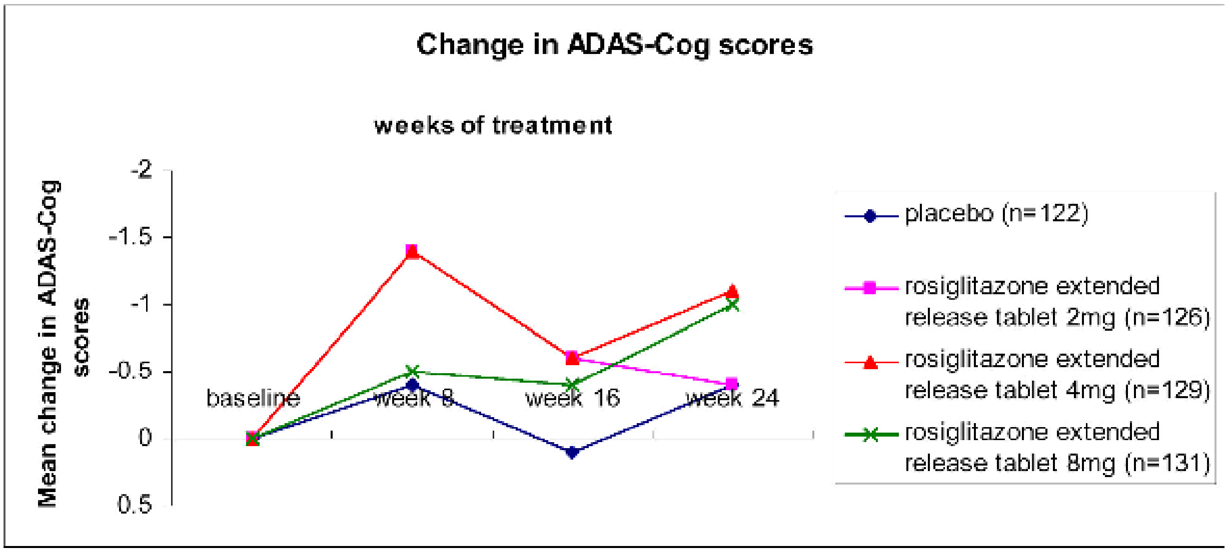
Background

Certain genes have been identified as risk factors in the progression of Alzheimer's disease (AD).(168) The gene Apolipoprotein E (APOE), which carries cholesterol through the bloodstream, has three common alleles (ε2, ε3, ε4) and genetic studies have demonstrated an association between patients who are positive for the ε4 variation of APOE and late-onset AD.(168,169,170) The APOE ε4 allele has been associated with an increased risk and earlier age-at-onset of AD, with those that are homozygous for APOE ε4 (two alleles of APOE ε4) having the greatest risk and earliest onset of the disease.(168)

Clinical Information

Risner et al conducted a 24-week double-blind, randomized, placebo-controlled study to evaluate the cognitive effects of rosiglitazone extended release tablets 2 mg (n = 127), 4 mg (n = 130), 8 mg (n = 132), or placebo (n = 122) in patients (mean age 70 years, range 50-85) with mild-to-moderate Alzheimer's disease (AD).(171) Patients included in the study were those who scored 16-26 on the Mini-Mental State Examination (MMSE). Patients were excluded from this study if any of the following applied: dementia secondary to causes other than AD, concurrent or recent treatment with cholinesterase inhibitors, selegiline, memantine, thiazolidinediones, or insulin, or history of Type I or Type II diabetes mellitus. Baseline characteristics were similar across treatment groups; mean baseline MMSE score was 21. Genotyping results were obtained for a total of 322 patients. Patients were stratified by APOE ε4 status with 179 ε4-negative patients and 140 ε4-positive patients. Primary endpoints at week 24 were mean change from baseline in ADAS-Cog and Clinician's Interview-Based Impression of Change Plus (CIBIC+) score, and results were also stratified by APOE genotype. Change from baseline in ADAS-Cog total scores in the intent-to-treat (ITT) population showed that treatment differences between rosiglitazone extended release tablets and placebo for ADAS-Cog total scores did not reach statistical significance at week 24 (last observation carried forward). Results are summarized in Figure 3. Rosiglitazone maleate extended release tablets have not been approved for marketing by FDA; therefore, no conclusions should be drawn about the safety or efficacy of rosiglitazone maleate extended release tablets at this time.

Figure 3. Effects of Rosiglitazone Extended Release Tablets on ADAS-Cog Scores* in ITT Population



*ADAS-Cog positive numbers indicate worsening and negative numbers indicate improvement

A prospectively defined exploratory analysis demonstrated a statistically significant result and the largest improvement in ADAS-Cog in APOE ε4-negative patients on rosiglitazone extended release tablets 8 mg ($P = 0.024$, not adjusted for multiplicity). APOE ε4-positive patients did not show improvement in any of the rosiglitazone treatment arms and showed the largest decline at the lowest rosiglitazone extended release tablet dose of 2 mg ($P = 0.012$, not adjusted for multiplicity). Results are summarized in Table 44.

Table 44. Results of Primary Efficacy End Point (ADAS-Cog) by APOE ε4 Carriage[171]

APOE ε4 carriage status (yes/no)	Treatment	N	Least-squares mean (s.e.)
No	placebo	43	1.10 (0.96)
	rosiglitazone extended release tablet 2 mg	49	-1.35 (0.90)*
	rosiglitazone extended release tablet 4 mg	45	-1.21 (0.90)
	rosiglitazone extended release tablet 8mg	42	-1.84 (0.95)*
Yes	placebo	35	-1.10 (1.04)
	rosiglitazone extended release tablet 2 mg	36	2.46 (1.03)*
	rosiglitazone extended release tablet 4mg	34	0.39 (1.05)
	rosiglitazone extended release tablet 8mg	36	0.39 (1.03)

*$P < 0.05$ vs. placebo: s.e. = standard error of the mean

CIBIC+ results were not reported as conditions were not met to proceed with hierarchical testing (failed co-primary endpoint) and no dose of rosiglitazone extended release tablets were determined to have a clinically meaningful effect.[171] Eighteen patients (3.5%) distributed evenly across treatment groups discontinued treatment before week 24 due to adverse events.[171] Most frequent treatment emergent adverse events are shown in Table 45.

Table 45. Most Frequent (≥ 3% in any group) Treatment Emergent Adverse Events(171)

	placebo (n = 124)	rosiglitazone extended release tablet 2 mg (n = 128)	rosiglitazone extended release tablet 4 mg (n = 131)	rosiglitazone extended release tablet 8 mg (n = 135)
Any event	44 (35%)	36 (28%)	41 (31%)	46 (34%)
Headache	6 (5%)	2 (2%)	1 (<1%)	3 (2%)
Diarrhea	4 (3%)	2 (2%)	2(2%)	3 (2%)
Nasopharyngitis	2 (2%)	1 (<1%)	4 (3%)	1 (<1%)
Edema peripheral	0	0	4 (3%)	3 (2%)

Serious adverse events were reported as follows: rosiglitazone extended release tablet 2 mg (6/128; 5%); rosiglitazone extended release tablet 4 mg (3/131; 2%, including one fatality owing to acute cardiac failure unrelated to study drug); rosiglitazone extended release tablet 8 mg (9/135; 7%); and placebo (7/124; 6%).

A 48-week open-label extension to the study by Risner et al was conducted that included subjects who had completed 24 weeks of treatment with no tolerability issues.(172) The primary objective of this study extension was to evaluate the long-term safety and tolerability of rosiglitazone extended release tablets in subjects with mild to moderate Alzheimer's disease. All subjects (n = 337) received one 4 mg extended release tablet daily for the first 4 weeks of treatment followed by one 8 mg extended release tablet daily for the remaining 44 weeks of treatment. The primary endpoint of the study was frequency of adverse events. A total of 163 subjects (48%) experienced an adverse event. The most frequently reported adverse events were peripheral edema, nasopharyngitis, anemia, and headache. A total of 26 subjects (8%) experienced any non-fatal serious adverse event (SAE) with the only SAE reported by more than one subject being femur fracture (2 subjects; 1%). Four deaths were reported during the treatment period. Secondary endpoints included change from baseline in ADAS-cog total score, CIBIC + score and Neuropsychiatric Inventory (NPI) total score. Due to the non-randomized, single-treatment study design, results are exploratory and intended to be hypothesis generating. The re-consented pharmacogenetics population in this study was also only 50% of those who consented in the 24 week study by Risner et al.

In a 24-week double-blind, placebo-controlled, randomized parallel-group study, Watson et al evaluated the effects of *Avandia* 4 mg/day (n = 20) and placebo (n = 10) on cognitive function in patients (mean age 73 years, range 55-85) diagnosed with early AD or amnestic mild cognitive impairment (MCI).(173) All patients were community-dwelling and scored ≥15 on the MMSE. Patients were excluded if they had neurological disorders other than AD or amnestic MCI or if they had diabetes mellitus. In patients receiving cholinesterase inhibitors, the dose had to be stable from 2 months prior to baseline and throughout the study. No patients were taking memantine or other medications known to affect cognition, central nervous system function, or glucose regulation. The primary cognitive outcome measures were assessed by the Buschke Selective Reminding Test and Story Recall. Secondary endpoints included measures of selective attention as per the Stroop Color-Word Interference. Relative to the placebo group, patients receiving *Avandia* exhibited better delayed recall at weeks 16 and 24 (per Buschke) and better selective attention at week 24 (per Stroop Color-Word Interference. Story recall did not statistically differ between treatment groups. *Avandia* was generally well tolerated and did not affect fasting glucose, lipid, aspartate aminotransferase, alanine aminotransferase levels, or body mass index (BMI). Reported adverse events included mild anemia (*Avandia* n = 3; placebo n = 1) and mild edema (*Avandia* n = 1). A cerebrovascular event, which was not considered to be attributed to study drug, was reported in one patient receiving *Avandia*.

8.6 Use of *Avandia* in the Treatment of Non-alcoholic Fatty Liver Disease (NAFLD)

Background

Non-alcoholic fatty liver disease (NAFLD) refers to a wide spectrum of liver damage ranging from simple steatosis to steatohepatitis (NASH), advanced fibrosis, and cirrhosis. (174) The proposed mechanism of hepatocyte damage in NAFLD involves insulin resistance, which leads to steatosis, and oxidative stress. Oxidative stress causes lipid peroxidation and activates inflammatory cytokines resulting in non-alcoholic steatohepatitis (NASH). (174) (175)

Effect of avandia on fatty liver or nash

Clinical Data

Ratziu et al conducted a randomized, double-blind, placebo controlled trial in patients with histologically proven non-alcoholic steatohepatitis (NASH).[176] The objective of this study was to assess whether *Avandia* improves liver disease in patients with NASH, if this improvement is associated with reduction in insulin resistance, and to identify a potential patient profile of response to thiazolidinediones. Patients aged 18-75 years with a histologic diagnosis of NASH and elevated alanine aminotransferase (ALT) levels, received either placebo (n = 31) or *Avandia* (n = 32) for 12 months and were followed up for 4 months after the end of treatment (EOT). *Avandia* 4 mg daily was escalated at the end of 30 days to 8 mg and was discontinued at the end of 12 months. Thirty-two percent of study population had diabetes.

The primary endpoint was a reduction in steatosis > 30% between baseline and EOT or disappearance of steatosis at EOT.[176] Secondary endpoints were normalization of serum ALT level at EOT and improvement in activity grade and/or liver fibrosis between baseline and EOT. A > 30% reduction in steatosis occurred more frequently in the *Avandia* group (47%; 15/32) than in the placebo group (16%; 5/31; $P = 0.014$). In the *Avandia* group, 6 subjects had reduction of 30%, 6 of 40%, and 3 of > 60% in percent steatosis from baseline to EOT compared to 3 of 30%, 1 of 40%, and 1 of 50% in placebo. One patient in the *Avandia* group and 2 patients in the placebo group progressed by 50%. Additionally, a statistically significant ($P = 0.02$) mean reduction in the steatosis histologic score between baseline and EOT was found in the *Avandia* (26%) and placebo (23%) groups. At the EOT, 12 patients in the *Avandia* group (38%) and 2 in the placebo group (7%) achieved normal ALT levels ($P = 0.005$). Overall, 20 patients in the *Avandia* group and 5 patients in the placebo group normalized ALT levels during treatment ($P < 0.001$). However, shortly after discontinuation, transaminases returned to baseline levels. There were no significant improvement in histological lesions, including fibrosis, hepatocyte ballooning, lobular inflammation/necrosis or mean variation of the composite nonalcoholic fatty liver disease activity score (NAS) in the *Avandia* treated patients. However, EOT liver biopsy specimens revealed several changes suggesting a favorable effect of *Avandia*. Additionally, improvement of steatosis correlated with reduction of transaminase levels ($r = 0.36$; $P < 0.005$), improvement in insulin sensitivity ($r = 0.34$; $P = 0.008$) and increase in adiponectin levels ($r = -0.54$; $P < 0.01$) but not with weight variations. Independent predictors of response were treatment with *Avandia*, the absence of diabetes, and massive steatosis.

Adverse events included swollen legs, muscular cramps, asthenia, significant weight gain (mean gain of 1.5 kg with *Avandia* and -1 kg with placebo; $P = 0.03$) and reductions in hemoglobin levels (mean loss of -0.65 g/dL with *Avandia* and -0.14 g/dL with placebo; $P = 0.01$).[176] Dose reduction due to side effects was necessary in 5 *Avandia* treated patients. One patient receiving *Avandia* discontinued treatment after 10 months due to pain associated with swollen legs.

Neuschwander-Tetri et al reported the results of an open-label trial of *Avandia* for the treatment of non-alcoholic steatohepatitis (NASH) in 30 adults. [177] NASH was diagnosed by a previous liver biopsy and an increased alanine aminotransferase levels (ALT) at screening. In addition to *Avandia*, 10 patients received a hydroxy-methyl-glutaryl coenzyme A reductase (HMG-CoA reductase) inhibitor and 2 patients were treated with a fibrate. At baseline, the mean age of the patients was 45.2 years and they had a mean weight of 100.3 kg. According to 2-hour oral glucose tolerance testing, 8 patients met the criteria for diabetes mellitus, 7 patients had impaired glucose tolerance, and 15 patients had normal glucose tolerance. A total of 5 patients did not complete the study. Pre-enrollment and post-treatment liver biopsies were evaluated in a blinded fashion. Unexpectedly, 7 patients did not meet the criteria for NASH at enrollment and were excluded from the analysis. For the remaining patients, treatment with *Avandia* resulted in significant improvements in clinical and histologic measurements (Table 1 and Table 2). Treatment with *Avandia* resulted in improved insulin sensitivity based on the mean quantitative insulin sensitivity check index (QUICKI) and homeostasis model assessment [(HOMA)-Insulin Resistance] measures. Histologic changes were not predicted by body mass index (BMI), age, gender, degree of ALT elevation or degree of insulin resistance. Weight gain occurred in 67% of patients with a mean increase of 6.4 kg. Following 48 weeks of treatment with *Avandia*, 10 out of 22 patients no longer met criteria for NASH.

Table 46. Biochemical Effects of *Avandia* (177)

BIOCHEMICAL CHANGES FROM BASELINE TO 48 WEEKS		
Biochemical Marker	Pre-Treatment (N=30)	Post-Treatment (N=25)
HbA1c (%)	5.7	5.3‡
ALT (U/L)	89	41*
AST (U/L)	60	34†
GGT (U/L)	96	36*
Total bilirubin (mg/dL)	0.6	0.6
Alkaline phosphatase (U/L)	98	65*
Triglycerides (mg/dL)	275	239
Cholesterol (mg/dL)	215	225
‡ $P = 0.015$; * $P < 0.001$; † $P = 0.003$ ALT = alanine aminotransferase; AST = aspartate aminotransferase; GGT = γ-glutamyl transpeptidase.		

Table 47. Histologic Effects of *Avandia* (177)

Histologic Parameter	Post-Treatment	*P* value
Global grade	Improvement - 13 patients	--
	No change - 7 patients	
	Worsening - 2 patients	
Steatosis (Amount)	Improvement - 14 patients	0.004
	No change - 11 patients	
	Worsening - 1 patients	
Hepatocellular Ballooning (Amount)	Improvement - 11 patients	0.003
	No change - 11 patients	
	Worsening - 1 patients	
Fibrosis (Score)	Improvement - 8 patients	0.583
	No change - 11 patients	
	Worsening - 3 patients	

Mizrak et al examined the role of insulin-sensitizing agents for the treatment of non-alcoholic steatohepatitis (NASH).[178] This prospective, randomized, longitudinal, single center study evaluated 62 subjects diagnosed with NASH for a period of 48 weeks (36 male; 26 female; mean age 46.2 years). Patients were randomized into 3 groups, which included conventional diet (25 kcal/kg times ideal body weight) and exercise (n = 23), diet and exercise with metformin 850 mg twice daily (n = 20), and diet and exercise with *Avandia* 8 mg once daily (n = 19). Baseline characteristics were well matched except for homeostasis model assessment-insulin resistance (HOMA-IR) estimates, which were higher in the *Avandia* group. At 48 weeks, liver biopsies were collected from 8 individuals in the diet and exercise group and 15 individuals from the *Avandia* and metformin groups. Compared to baseline, serum alanine aminotransferase (ALT) levels significantly decreased in all groups. Specifically, serum ALT decreased to normal levels in 68.4% of patients in the *Avandia* group, 40% in the metformin group, and 39% in the diet and exercise group. Compared to baseline, significant decrease in HOMA-IR estimates ($P < 0.01$) and non-alcoholic fatty liver disease activity scores [(NAS); $P < 0.03$] were reported in the *Avandia* and metformin groups (Table 48). NAS is comprised of 14 histological features which addresses the full spectrum of lesions of non-alcoholic fatty liver disease (NAFLD).[179] Also, a significant decrease in body mass index (BMI) was noted in the metformin treated group ($P < 0.0001$). No serious adverse events related to insulin-sensitizing agents were reported.

Table 48. Effects of Insulin-Sensitizing Agents on ALT, HOMA-IR, and NAS (178)

	Diet and exercise plus *Avandia* (n = 19)	**Diet and exercise plus metformin (n = 20)**	**Diet and exercise (n = 23)**
Mean Serum ALT (IU/L) Pre-Treatment	78	76.3	66.4

	Diet and exercise plus *Avandia* (n = 19)	**Diet and exercise plus metformin (n = 20)**	**Diet and exercise (n = 23)**
Mean Serum ALT (IU/L) Post-Treatment	41.0*	51.5*	41.3*
HOMA-IR Pre-Treatment	5.7	4.6	--
HOMA-IR Post-Treatment	2.5*	3*	--
NAS Pre-Treatment	5	5	4.4
NAS Post-Treatment	3.8†	3.8†	4.5
* $P < 0.01$ vs. baseline; † $P < 0.03$ vs. baseline. ALT = Alanine aminotransferase; HOMA-IR = Homeostasis model assessment-insulin resistance; NAS = Non-alcoholic fatty liver disease activity score.			

Similarly, results from a head-to-head study, comparing the effects of *Avandia*, metformin, and a combination of *Avandia* and metformin in type 2 diabetic patients with NAFLD showed improved HOMA-IR estimates and NAFLD scores in subjects treated with *Avandia* containing regimens.(180)

Please note, data should be interpreted with caution as abstracts frequently present limited data and are sometimes based on early analysis. Information regarding study design and all pertinent data may not have been included in the abstracts.

8.7 The APPROACH Trial

APPROACH

The *A*ssessment on the *P*revention of *P*rogression by *R*osiglitazone *O*n *A*therosclerosis in diabetes patients with *C*ardiovascular *H*istory (APPROACH) is a randomized, active-control, double-blind international trial that evaluated the effect of *Avandia* on the progression of atherosclerosis as assessed by intravascular ultrasound (IVUS), in patients with and evidence of cardiovascular (CV) disease.(181) Patients were randomized to receive either *Avandia* (n = 333) or glipizide (n = 339) for 18 months.(182) The primary endpoint of this trial was the percent atheroma volume (PAV) change from baseline to 18 months as measured by IVUS. Secondary trial outcomes included other angiographic and IVUS-derived atherosclerotic endpoints, CV events, lipids, and CV biomarkers.

Patients with type 2 diabetes and a clinically indicated coronary angiographic or percutaneous intervention (PCI) with at least one atherosclerotic plaque in a nonintervened coronary artery with 10% to 50% luminal narrowing were included in the study. The HbA1c at baseline was > 7% and ≤ 10% (if treated with diet and exercise only) or > 6.5% and ≤ 8.5% (if treated with oral antidiabetic medications). Patients were excluded from the study for reasons that included coronary artery bypass graft (CABG) surgery, uncontrolled hypertension, left ventricular ejection fraction < 40%, or heart failure (New York Heart Association Class I-IV).

Patients were randomized to receive either *Avandia* or glipizide with starting doses of 4 mg and 5 mg, respectively. As the study medications were initiated, the prior therapy was discontinued after one month. By week 12, doses were titrated up to a maximal total daily dose of *Avandia* 8 mg and glipizide 15 mg as tolerated. After the first 3 months, metformin with a maximum daily dose of 2550 mg and once daily insulin or both were added if necessary to maintain HbA1c < 7% using a glycemic titration algorithm. Statin use was encouraged among participants to reach the National Cholesterol Education Program-Adult Treatment Panel III (NCEP-ATP III) goal for low-density lipoprotein cholesterol targets (LDL-C) of < 100 mg/dL or < 70 mg/dL as determined by the investigator. In addition, patients used antihypertensive, antiplatelet, and antithrombotic agents in compliance with clinical guidelines. Please refer toTable 49 for baseline demographic and disease characteristic information.

Table 49. Baseline Demographics, Disease Characteristics, Medications, and Laboratory Values[181]

	N = 672
Age (years)	61.0
Male (%)	67.7
Body mass index (kg/m^2)	29.5
HbA1c (%)	7.2
Median diabetes duration (years)	4.8
Hypertension (%)	79.9
Dyslipidemia (%)	68.0
Prior myocardial infarction (%)	24.0
Blood pressure (mmHg)	129/76
Low-density lipoprotein cholesterol (LDL-c) (mg/dL)	90.3
High-density lipoprotein cholesterol (HDL-c) (mg/dL)	43.0
Triglycerides (mg/dL)	160.6
Nitrates (%)	39.0
Statin (%)	75.9
Aspirin (%)	83.2
hsCRP (mg/L)	5.1

For the primary endpoint, treatment with *Avandia* resulted in a -0.21 % (P = 0.53) mean decrease in atheroma volume from baseline at 18 months. Treatment with glipizide resulted in a mean increase in PAV of 0.43 (P = 0.19) from baseline. The mean treatment difference compared to glipizide was -0.64 % (95% Confidence Interval [CI] -1.46, 0.17; P = 0.12) at 18 months. Treatment effects on secondary endpoint measures of atheroma volume are included in Table 50.

Table 50. Treatment Effects on Atheroma Volume[182]

	Avandia n = 233	**Glipizide** n = 229
PAV - Primary Endpoint		
Change from baseline, %	-0.21 P = 0.53	0.43 P = 0.19
Treatment difference, %	-0.64 95% CI -1.46, 0.17 P = 0.12	
Total Atheroma Volume (normalized)*		
Change from baseline, mm^3	-3.9 P = 0.05	1.2 P = 0.54
Treatment difference, mm^3	-5.1 95% CI -9.98, -0.26 P = 0.04	
Atheroma Volume in 10 mm Most Diseased Segment*		
Change from baseline, mm^3	-5.3 P < 0.0001	-3.6 P < 0.0001
Treatment difference, mm^3	-1.7 95% CI -3.93, 0.49 P = 0.13	
* Secondary endpoint. CI = Confidence interval; PAV = Percent atheroma volume.		

Changes in metabolic parameters from baseline were measured following 18 months treatment with *Avandia* and glipizide. (Please see Table 51)

Table 51. Changes in Metabolic Parameters (IVUS Evaluable Population) (182)

Change from Baseline	*Avandia* n = 233	Glipizide n = 229	*P-Value*
HbA1c (%)	-0.3	-0.2	0.44
LDL-c (mg/dL)	2.8	-7.8	0.002
HDL-c (mg/dL)	6.2	2.6	<0.001
Triglycerides (mg/dL)	-14.2	-8.9	0.16
Weight (kg)	2.6	1.4	0.02
HDL-c = High-density lipoprotein cholesterol; IVUS = Intravascular ultrasound; LDL-c = Low-density lipoprotein cholesterol.			

There were no significant differences between treatment groups with respect to adjudicated CV outcomes (including CV death, myocardial infarction, and stroke, Table 52).

Table 52. Adjudicated Cardiovascular Events(182)

Patients, n (%)	*Avandia* n = 333	Glipizide n = 339	*P-Value*
Composite of all-cause death, nonfatal MI, nonfatal stroke, coronary revascularization, or hospitalization for myocardial ischemia	39 (11.7%)	38 (11.2%)	0.58
Composite of CV death, nonfatal MI, nonfatal stroke	14 (4.2%)	10 (2.9%)	0.31
All-cause death	8 (2.4)	7 (2.1%)	0.72
Cardiovascular death	4 (1.2%)	3 (0.9%)	0.50
Myocardial infarction, non-fatal	7 (2.1%)	6 (1.8%)	0.71
Myocardial infarction, fatal	1 (0.3%)	1 (0.3%)	0.89
Stroke, non-fatal	5 (1.5%)	1 (0.3%)	0.13
Stroke, fatal	0	0	-
Coronary revascularization	26 (7.8 %)	27 (8.0%)	0.82
Hospitalization for myocardial ischemia	11 (3.3 %)	7 (2.1%)	0.25
Congestive heart failure	8 (2.4%)	3 (0.9%)	0.14

Bone fracture and decreased hemoglobin were reported more frequently with *Avandia*. Hypoglycemia was more frequent with glipizide. Please refer toTable 53 for additional information regarding adverse events.

Table 53. Adverse Events(182)

	Avandia n = 333	Glipizide n = 339	*P-Value*
Bone fracture	6 (2%)	2 (<1%)	0.17
Peripheral edema	29 (9%)	24 (7%)	0.48
Hypoglycemia	27 (8%)	96 (28%)	<0.0001
Severe hypoglycemia (requiring external assistance)	0 (0%)	3 (<1%)	0.25
Angina pectoris	31 (9%)	35 (10%)	0.69
Hemoglobin decrease > 3 g/dL	26 (8%)	10 (3%)	0.01
ALT > 3 x upper limit of normal	2 (<1%)	3 (<1 %)	1.00

9. OUTCOME AND ECONOMIC EVALUATION

Background

An estimated 20.8 million Americans are affected by diabetes. (1) Type 2 diabetes accounts for 90 to 95% of all diagnosed diabetes cases and affects more than 18 million people in the United States. (183) The American Diabetes Association (ADA) has estimated the total cost (direct and indirect) attributable to diabetes to be $132 billion in 2002. (1) Over two-thirds of these costs were direct medical costs such as those due to hospitalization, outpatient visits, and the rest were indirect costs such as those due to lost productivity.

Health problems from diabetes are a serious issue in the U.S. (183) The State of Diabetes Complications in America report shows that 3 out of 5 people with type 2 diabetes has at least one of the serious health problems connected to the disease such as, heart disease, stroke, eye damage, kidney disease, and foot problems that can lead to amputation. Estimated annual healthcare costs for a person with diabetes and its related complications are about three times that of the average American without diagnosed diabetes.

Large-scale studies have demonstrated that tight glycemic control greatly reduces the frequency and severity of long-term diabetes-related complications. In the 10-year United Kingdom Prospective Diabetes Study (UKPDS), intensive glycemic control resulted in HbA1c levels that were significantly lower than in patients on conventional therapy.(184) According to the UKPDS 35 Study, every 1% decrease in HbA1c resulted in a 21% decrease in risk of any diabetes-related end point. (185) The primary goal of diabetes therapy should be to prevent the occurrence of diabetic complications by enhanced glycemic control and treatment of insulin resistance.

Treatment Adherence with *Avandia*

A retrospective cohort study was conducted using patient data from the North Carolina Medicaid program database queried from July 1, 2001 to June 30, 2002.(19) Patients were followed up for complete healthcare service utilization (hospitalizations, emergency department visits, outpatient physician visits, utilization of antidiabetic medication) and costs. Measures of adherence (medication possession ratio) and persistence (index of treatment persistence) were used to assess utilization of antidiabetic medication. Total annual healthcare costs were compared for Medicaid recipients newly started on thiazolidinediones (TZDs) vs. other oral antidiabetic agents. When healthcare costs were compared for Medicaid recipients newly started on TZDs vs. other oral antidiabetic agents, cost savings were realized for the TZD cohort as early as 2 years following therapy initiation (\$9,458 vs. \$10,629, $P < 0.05$). Patients starting TZDs had 16% lower total annual healthcare costs compared to patients starting other oral antidiabetics ($P < 0.01$). The persistence and adherence rates for the TZD group were statistically significantly higher than the oral antidiabetics group at nearly 9% and 13%, respectively ($P < 0.01$). The subanalysis comparing the two TZDs, *Avandia* and pioglitazone, showed no significant differences between the two TZD groups in total annual healthcare costs, treatment adherence, or persistence rates.

An extended analysis was conducted to examine the original cohort of patients for an additional 18 months (up to December 2004) of observational follow-up. (186) Average healthcare costs for patients on a TZD were less compared to the metformin and other sulfonylurea groups ($P < 0.05$). Overall, TZD's were associated with improved adherence but not persistence.

A separate analysis utilizing the same Medicaid database compared healthcare utlilization and costs associated with initiation of treatment with either *Avandia* or pioglitazone in type 2 diabetes patients. (187) *Avandia* monotherapy was associated with a 12.2% decrease in the mean number of hospitalizations, a 10.4% decrease in mean number of emergency department visits, and 7.3% decrease in total healthcare costs compared with the pioglitazone monotherapy group ($P < 0.05$ for all comparisons).

Resource Utilization and Cost of Care with *Avandia*

The RESULT (Rosiglitazone Early vs. SULfonylurea Titration) trial demonstrated that combination therapy of *Avandia* and a sulfonylurea (SU; glipizide) has potential to reduce health service utilization and cost of care in type 2 diabetes if compared to progressive titration of an SU (glipizide). (188) In this study, patients on glipizide 10 mg twice daily were randomized to the addition of *Avandia* (4 mg once daily to 8 mg once daily as needed) before titration of glipizide, or to continued up-titration of glipizide, to a maximum of 40 mg/day. Over a 2-year study period, in addition to superior glycemic control, combination therapy with *Avandia* and SU was associated with significantly fewer emergency department (ED) visits (0.59 vs. 1.47 per 1000 patient-days, $P = 0.0006$) and hospitalizations (0.37 vs. 0.76 per 1000 patient days, $P = 0.0263$) compared to SU monotherapy. Despite higher pharmacy costs, total direct per patient per month (PPPM) healthcare costs were also significantly lower with *Avandia* and SU therapy compared to SU monotherapy (\$480 vs. \$645 PPPM, $P < 0.05$).

A 12-month analysis of administrative records of Medicaid beneficiaries initiating therapy with TZDs or insulin demonstrated that patients receiving TZDs incurred higher diabetes-related pharmacy costs ($1,678 vs. $1,096, $P < 0.01$), which where offset by lower costs for ER visits and hospitalization in the TZD group as compared to insulin group ($2,855 vs. $5,090, $P < 0.01$), resulting in significantly lower total type 2 diabetes-related medical costs associated with pioglitazone or *Avandia* ($5,425 vs. $7,255, $P < 0.05$).[189]

10. ECONOMIC MODEL

Avandia: ECONOMIC MODEL

Purpose

The purpose of the budget impact model is to determine the impact of changes in market distribution for *Avandia* and Actos® (pioglitazone, Takeda Pharmaceuticals) on a State Medicaid pharmaceutical budget. This information will help decision-makers understand the impact of changes in utilization of the two oral antidiabetic drugs in a population of patients with type 2 diabetes. The overall objective of this model is to estimate the economic impact of the adoption of *Avandia* compared to pioglitazone under a pre-defined utilization scenario in the State Medicaid population.

Methods

This model was developed by GlaxoSmithKline using Microsoft Excel. It evaluates drug costs in type 2 diabetes patients for two different thiazolidinediones (*Avandia* and pioglitazone) based on wholesale acquisition cost (WAC), daily average consumption (DACON) numbers, and the distribution of the population taking each dose combination. WAC is the listed price to wholesalers and warehousing chains, not including prompt pays, stocking or distribution allowances, or other discounts, rebates or charge backs. DACON was defined as the number of tablets consumed by each patient per day.

The following parameters are used in the model:

1. The total number of people in the State Medicaid population (n = 500,000).
2. The prevalence of diagnosed diabetes (the default is 6%).
3. The prevalence for Type 2 diabetes (the default is 90%).
4. The percentage of Type 2 diabetes patients who take thiazolidinediones (the default is 30%).
5. The pricing information for each drug (the default is WAC, Wolters-Kluwer, January 2007).
6. The distribution of patients according to the dosage form of each drug (the default is based on DACON estimates from NDC Health Rolling 3 months average, November 2006).
7. The percentage of patients taking each drug before and after changes in market distribution (Table 54).

Model results are automatically generated upon entry of the information in steps 1-7. These estimates will vary based on the assumptions made regarding prescribing patterns and utilization trends within the State Medicaid population.

Table 54. Percentage of Patients on Each Product (Hypothetical Distribution)

	Beginning Market Share	Ending Market Share
Avandia	50%	90%
Pioglitazone	50%	10%

Table 55 below illustrates the average cost per person per day of *Avandia* and pioglitazone. For these particular combinations, the following assumptions were made:

Wholesale Acquisition Cost of *Avandia*

- 2 mg: $2.04/tablet
- 4 mg: $3.03/tablet
- 8 mg: $5.51/tablet

Wholesale Acquisition Cost of pioglitazone

- 15 mg: $3.25/tablet
- 30 mg: $5.21/tablet

- 45 mg: $5.65/tablet

The key cost savings from this model are derived from the combination of daily average consumption DACON and the WAC per tablet. For any *Avandia* dose, the DACON is greater than the relatively equivalent pioglitazone dose. Given the individual tablet cost is greater at every equivalent dose with pioglitazone than with *Avandia*, the average daily drug cost for *Avandia* is always less than pioglitazone.

Table 55. Average Cost Per Day of Thiazolidinediones

	DACON	$Cost/tablet	Average $Cost/person/day
Avandia			
2 mg	1.6	$2.04	$3.26
4 mg	1.4	$3.03	$4.24
8 mg	1.1	$5.51	$6.06
Pioglitazone			
15 mg	1.1	$3.25	$3.58
30 mg	1.1	$5.21	$5.73
45 mg	1.1	$5.65	$6.22

Key Assumptions

The scenario presented below includes assumptions that were developed from product information and published literature. First, it was assumed that there are 500,000 Medicaid enrollees in the State. The prevalence of diabetes among them was assumed to be 6%. The vast majority (90%) were assumed to have type 2 diabetes, of whom 30% were using a thiazolidinedione.

Model Results

The thiazolidinedione market scenario provides results that exhibit the comparative costs between *Avandia* and pioglitazone. The distribution of patients on *Avandia* 2 mg, 4 mg, and 8 mg tablets was 11%, 55%, and 34%, respectively. The distribution of patients on pioglitazone 15 mg, 30 mg, and 45 mg tablets was 26%, 39%, and 35%, respectively. The beginning patient percentages of *Avandia* (50%) and pioglitazone (50%) reflect the current distribution of the two drugs in the market. The ending patient percentages for each product (90% for *Avandia* and 10% for pioglitazone) reflect the hypothetical shift in market share.

Table 56 summarizes the economic impact given the assumptions of the model with a cohort of 8,100 patients with type 2 diabetes on oral antidiabetic agents distributed evenly between *Avandia* and pioglitazone. Differences in costs were estimated for both *Avandia* pioglitazone and are summarized below.

Table 56. Estimated Total Economic Impact for Medicaid Population

	Beginning Population Distribution	Beginning Cost to Medicaid	Ending Population Distribution	Ending Cost to Medicaid	Cost Savings
Avandia	50%	$7,100,986	90%	$12,781,775	
Pioglitazone	50%	$7,908,572	10%	$1,581,714	
Totals		*$ 15,009,558*		*$ 14,363,489*	**$646,069**
					4.30%

Using WAC as a default, the use of *Avandia* compared to pioglitazone may result in a significant decrease in Medicaid pharmacy expenditures. Assuming market share approximates the current national market distribution (i.e. 50/50), there is a $807,586 difference between the overall costs of *Avandia* and pioglitazone (Table 3, column 3). After the hypothetical shifts in market share (Table 3, column 4), the model estimates pharmacy costs for *Avandia* to be $12,781,775 per year, while pharmacy costs would be approximately $1,581,714 for pioglitazone. This represents an overall reduction in pharmacy costs of $646,069 or 4.30%.

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